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(54) Title: AN ANTISENSE OLIGONUCLEOTIDE PREPARATION METHOD

(57) Abstract

A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of: selecting a target nucleic acid, if necessary elucidating its sequence; generating the antisense oligonucleotide with the proviso that: the oligonucleotide comprises at least 8 residues; the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases; the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG; the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG; and the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications: $3\text{H-bond-R}/3\text{H-bond-R} + 2\text{H-bond-R} \geq 0.29$; and synthesizing the oligonucleotide thus generated in a per se known manner.

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An antisense oligonucleotide preparation method

The present invention is related to a method for the preparation of antisense oligonucleotides and to an oligonucleotide or functional or structural analogs or effective derivatives thereof, forming hydrogen bonds with deoxyribonucleic acids (DNA) and/or ribonucleic acids (RNA) or derivatives thereof including, but not limited to the formation of hydrogen bonds with the bases adenine (A), cytosine (C), guanine (G), uracil (U) or thymidine (T) contained in such molecules or forming hydrogen bonds with residues of a particular protein, such a molecule being capable of altering the expression structure or function, of a gene, an RNA molecule or a protein or altering the level of activity of a gene, an RNA molecule or a protein. Furthermore, the present invention is related to such nucleic acid or functional or structural analogs or effective derivatives thereof, coupled or mixed with folic acid, hormones, steroid hormones such as oestrogen, progesterone, corticosteroids, mineralocorticoids, androgens, peptides, proteoglycans, phospholipids, glycolipids and derivatives therefrom.

Furthermore, the invention is related to the use of said nucleic acids or functional or structural analogs or effec-

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tive derivatives thereof, for analyzing the functional properties of a particular gene, RNA, or protein by altering its activity, structure, function or altering its expression levels.

Furthermore, the invention is related to antisense nucleic acids, capable of modulating the expression or functional activity of proteins which regulate cell growth leading to augmentation, inhibition or modulation of cell growth or cell proliferation and/or the expansion of primary cells or stem cells, e.g. in culture or in the living organism.

Furthermore, the invention is related to a pharmaceutical composition comprising said nucleic acids or functional or structural analogs or effective derivatives thereof, hybridizing with an area of the messenger RNA (mRNA) or the DNA of a target gene or binding to a particular protein as well as the use of said nucleic acids, structural analogs and derivatives thereof for the manufacturing of a pharmaceutical composition for the treatment of diseases where the alteration of the structure function, activity or expression of a particular target gene, a particular target RNA or a particular target proteins activity leads to a therapeutic benefit related to the effect of the nucleic acid or derivative thereof.

Modulation of the expression of genes, RNA molecules or proteins or of their activity levels with nucleic acids or functional or structural analogs or effective derivatives thereof is a powerful means to study the function of the respective molecules. For example modulation, e. g. knockdown or increase of the expression of a particular protein can lead to the identification of its physiological as well as its pathophysiological roles in cultured cells as well as in living organisms *in vivo*.

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Furthermore, the aberrant expression or overexpression of genes, RNA molecules or proteins, the expression of foreign DNA, RNA or proteins e. g. derived from infectious organisms or the expression of mutated DNA, RNA and proteins is found in a variety of diseases. Downregulation of the expression or the activity of such DNA, RNA and/or proteins can lead to an inhibition of or to the reversal of pathological processes in which the expression of a particular DNA, RNA and/or protein plays a role. However, nucleic acids or derivatives thereof used for downregulation of DNA, RNA and/or protein expression are often ineffective and/or toxic to the cells or the organisms treated with such molecules.

An object of the present invention is to provide a method for designing and preparation of oligonucleotides or derivatives thereof which avoid the drawbacks of prior art, and give a reliable method for preparation of oligonucleotides having increased effectiveness and/or reduced toxicity and/or reduced non-selective effects.

The object is attained by a method having the features of claims 1. Preferred embodiments of the method of the invention are those according to claims 2 to 7.

The method of the invention comprises the steps

- of selecting a target nucleic acid, if necessary elucidating its sequence
- generating the antisense oligonucleotide with the proviso that
 - the oligonucleotide comprises at least 8 residues,
 - the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases,

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- the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG,
- the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG, and
- the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications:

$$\frac{3\text{H-bond-R}}{3\text{H-bond-R} + 2\text{H-bond-R}} \geq 0.29$$

- and synthesizing the oligonucleotide thus generated in a per se known manner.

The generated antisense oligonucleotide comprises at least 8 residues in order to have sufficient interaction with the target molecule and has preferably up to 30, more preferably up to 24 or most preferred up to 18 residues. Shorter chain length are preferred over longer ones to increase specificity and/or reduce non-specific effects.

The oligonucleotide comprises at maximum 12 elements which are capable of forming 3 hydrogen bonds each to cytosine bases. In case of generating an oligonucleotide an element is represented by a residue, thus a nucleotide of the oligo-

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nucleotide. In cases of generating a derivative an element is considered as a part of the molecule capable of forming hydrogen bonds. It is preferred that the oligonucleotide comprises at maximum 10 and more preferred at maximum 8 elements which are capable of forming 3 hydrogen bonds each to cytosine bases.

The generated antisense oligonucleotide preferably does not contain 4 or more consecutive guanine bases and does also not contain 2 or more series of 3 consecutive guanine bases.

Preferably, the ratio between residues forming 2 hydrogen bonds per residue (2H-bond-R) with their target molecule and those residues forming 3 hydrogen bonds per residue (3H-bond-R) :

$$\frac{3\text{H-bond-R}}{3\text{H-bond-R} + 2\text{H-bond-R}}$$

is in the range of greater than 0.33 and smaller than 0.86, more preferably smaller than 0.79 and still more preferred smaller than 0.72.

In one embodiment the oligonucleotides generated by the method of the invention are modified for higher nuclease resistance than naturally occurring nucleotides. Methods for synthesizing oligonucleotides and derivatives thereof are known in the art, see for example "Oligonucleotides and Analogues", F. Eckstein (Ed.), 1991, IRL Press Oxford or "Protocols for Oligonucleotides and Analogs, Synthesis and Properties", Sudhir Agrawal (Ed.), 1993, Humana Press, Totowa, New Jersey.

Oligonucleotides of the invention may also contain RNA and DNA residues within their chains.

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The modifications can be made to the bases, the sugars or the linkages of the oligonucleotides. Preferably, the modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar moiety or modifications of the bases. In a preferred embodiment the oligonucleotide has at least two different types of modifications and more preferably at least two different types of internucleotide linkages. In another preferred embodiment the oligonucleotides are linked to or mixed with folic acid, hormones such as steroid hormones or corticosteroids, peptides, proteoglycans, glycolipids, phospholipids or derivatives thereof.

Surprisingly the molecules, obtainable according to the method of the invention could strongly reduce or avoid toxicity and/or non-specific effects of such molecules and/or had significantly higher activity than sequences selected otherwise. Preferably, the molecules according to the invention have the following features: They do not contain four or more consecutive guanosine (N_aGGGN_b) or inosine (N_aIIIIN_b) residues and the oligonucleotide does not contain two or more series of three or more consecutive guanosine residues ($N_aGGGN_cGGGN_b$) and does not contain two ore more series of three or more consecutive inosine residues ($N_aIIIN_cIIIN_b$), wherein N_a , N_b , N_c represent indepently oligonucleotides of any sequence having 0 to 20 residues.

In a preferred embodiment the molecule contains a minimum of 10 residues capable of forming either two or three hydrogen bonds per residue. Furthermore, the molecule contains a maximum of 24 consecutive residues linked by phosphorothioate linkages capable of forming either two or three hydrogen bonds per residue. In molecules according to the invention which contain more than 18 residues the additional

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linkages preferably consist of methylphosphonate linkages or phosphodiester linkages.

The chemical structures of antisense oligodeoxy-ribonucleotides are given in figure 1.

The chemical structures of antisense oligo-ribonucleotides are given in figure 2. The oligonucleotide is to be understood as a detail out of a longer nucleotide chain.

Of course, the oligonucleotides may be composed of elements of either figures.

In figures 1 and 2, lit. B means an organic base such as adenine (A), guanine (G), cytosine (C), inosine (I), uracil (U) and thymine (T) which are coupled to the deoxyribose. The linkages between the nucleotides are either phosphodiester bonds as in naturally occurring DNA or linkages spacing the nucleotides in such a way to allow hybridization with its target nucleic acid or binding to a protein in order to regulate its activity, such as e.g. phosphorothioate linkages, methylphosphonate linkages, phosphoramidate linkages or peptide linkages.

R₂ and R₃ represent further residues of the oligonucleotide or derivative.

R₄ represents OH or a modification such as a 2'-methoxy ethoxy derivative.

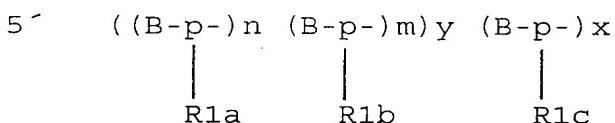
The modifications of the phosphodiester linkage, shown in figures 1 and 2 can be selected from, but are not limited to.

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1. Oligodeoxy-ribonucleotides or oligoribonucleotides substituted by

- 1.1 R₁ = O
- 1.2 R₁ = S
- 1.3. R₁ = F
- 1.4. R₁ = CH₃
- 1.4. R₁ = OEt

2. Oligodeoxy-ribonucleotides where R₁ is varied at the internucleotide phosphates within one oligonucleotide



where lit. p stands for the phosphodiester or the phosphoramidate linkage, modified by coupling to R_{1a}, R_{1b} or R_{1c} or for a peptide linkage, or for linkages spacing the nucleotides in such a way to allow hybridization with its target nucleic acid or binding to a protein in order to regulate its activity, structure, function or expression level.

where lit. B = any deoxy-ribonucleotide or ribonucleotide , depending on gene sequence according to the invention.

n, m, x, y = integers 0 - 20

Preferred maximal length of the total number of bases is 30.

2.1	R _{1a} = S	R _{1b} =CH ₃	R _{1c} =S
2.2	R _{1a} = S	R _{1b} =CH ₃	R _{1c} =O
2.2	R _{1a} = S	R _{1b} =O	R _{1c} =S
2.2	R _{1a} = S	R _{1b} =O	R _{1c} =CH ₃
2.3	R _{1a} = CH ₃	R _{1b} =S	R _{1c} =CH ₃
2.4	R _{1a} = CH ₃	R _{1b} =S	R _{1c} =O
2.5	R _{1a} = CH ₃	R _{1b} =O	R _{1c} =CH ₃
2.6	R _{1a} = CH ₃	R _{1b} =O	R _{1c} =S

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2.7	R _{1a} = O	R _{1b} =S	R _{1c} =O
2.8	R _{1a} = O	R _{1b} =S	R _{1c} =CH ₃
2.9	R _{1a} = O	R _{1b} =CH ₃	R _{1c} =O
2.10	R _{1a} = O	R _{1b} =CH ₃	R _{1c} =S

Preferably, the oligonucleotide comprises a minimum of 10 elements and a maximum of 24 elements capable of forming either 2 or 3 hydrogen bonds per element. The oligonucleotides of the invention can have modifications to the base, the sugar or the phosphate moiety. Preferred modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases. In a very preferred embodiment the antisense oligonucleotides comprise the sequences 41 to 73, 74 to 106, 154 to 172, 173 to 203, 298 to 380, 476 to 506, 519 to 556 and 597 to 641 of figure 3 and 1273 - 1764 of figure 5. A further aspect of the invention is the use of the oligonucleotides of the invention for the inhibition of the genes p53, rb, junD, junB, TGF- β 1, TGF- β 2 to influence cell proliferation, in particular of primary cell cultures such as liver cells, kidney cells, osteoclasts, osteoblasts and/or keratinocytes and/or cells of the blood lineage, such as bone marrow stem cells, and/or progenitor cells of red and white blood cells and/or organ stem cells.

The Sequences 41 - 73 and/or 74 - 106 and/or 154 - 203 and/or 519 - 556 and/or 597 - 641 and/or 1273 - 1277 and/or 1481 - 1490 and/or 1532 - 1549 and/or 1656 are useful for the treatment and/or prevention of immunosuppressive disorders including, but not limited to immunosuppression in neoplastic diseases - including gliomas and other brain tumors, sarcomas, carcinomas and lymphomas - and/or immunosuppression as side effect from drugs, including, but not limited to side effects from cytotoxic agents and/or immunosuppression in AIDS patients.

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In a further embodiment of the invention these sequences are also useful for the treatment and/or prevention of hyoproliferation of normal cells, including, but not limited to immune cells, bone marrow stem cells, endothelial cells, organ stem cells and proliferating cells of the intestine.

The Sequences 41 - 73 and/or 74 - 106 and/or 298 - 380 and/or 476 - 506 and/or 519 - 556 and/or 1273 - 1480 and/or 1596 - 1614 and/or 1657 - 1658 and/or 1690 and/or 1696 - 1712 and/or 1751 and/or 1753 - 1754 and/or 1757 are useful for the treatment and/or prevention of hyperproliferative disorders, including but not limited to brain tumors, sarcomas, carcinomas and lymphomas, restenosis, hyperplasia, pulmonary fibrosis, angiogenesis and psoriasis.

The Sequences 1278 - 1480 and/or 1491 - 1531 and/or 1582 - 1595 and/or 1615 - 1655 and/or 1691 - 1694 and/or 1697 - 1750 and/or 1759 - 1764 are useful for the treatment and/or prevention of diseases characterised by hyperfunction of the immune system and/or of inflammatory disorders and/or autoimmune disorders, including, but not limited to asthma (molecules according to the invention being applied by inhalation and/or by parenteral routes and/or orally), multiple sclerosis, inflammatory disorders of the intestine, including jejunitis, ileitis and/or colitis, as well as inflammatory disorders characterised by hyperproliferation and/or hyperfunction of cells of the eosinophilic lineage and/or glomerulonephritis and/or rejection of transplants.

The Sequences 476 - 506 and/or 1550 - 1581 and/or 1582 - 1595 and/or 1658 - 1689 and/or 1691 - 1694 and/or 1713 - 1752 are useful for the treatment and/or prevention of diseases associated with cell degeneration, including, but not limited to neurodegeneration, e.g. Alzheimer's diseases, Parkinson's, ischemic disorders, including myocardial ischemia and/or ischemia of the nervous system, including stroke.

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A further aspect of the present invention is a medicament comprising an oligonucleotide according to the invention together with additives. The oligonucleotides of the invention can be used for the preparation of a medicament for the prevention or the treatment of neoplasm, hypoproliferation, hyperproliferation, degenerative diseases, neurodegenerative diseases, ischaemia, disorders of the immune system and/or infectious diseases and can be used for the analysis of gene function or drug target validation.

Molecules according to the invention can be used to study the function of target molecules and their encoded transcription and/or translation products, including RNA molecules and proteins. Downregulations of a protein or nucleic acid molecule using molecules according to the invention can be used to study the function of the molecule. It is also a feature of the invention that molecules according to the invention can be used to study whether modulation of the product has a desired effect, including therapeutic effects and to use this information to develop a different molecule, in order to modulate the function of the protein.

This includes, for example, drug target validation with a molecule according to the invention, in order to answer the question whether development of an agent capable of modulating the structure, function or expression of a potential target molecule, e. g. an agonist or antagonist of the target molecule has desired effect and may e. g. be of therapeutic or diagnostic use.

It is thus also a feature of the invention that molecules according to the invention can be used for drug target validation, including but not limited to studying whether modulation of a protein or nucleic acid molecule has a desired effect, including therapeutic effects and using this information to develop a compound, e. g. a therapeutic compound capable of modulating the structure, function or

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expression of the molecule the function of which was previously studied with molecules according to the invention.

Example 1

Treatment of Peripheral blood mononuclear cells with TGF- β 1 antisense phosphorothioate oligodeoxynucleotides:

Human peripheral blood mononuclear cells (PBMCs) produce transforming growth factor β 1 (TGF- β 1). The TGF- β 1 produced by these cells negatively regulates immune cell proliferation in an autologous manner. This autologous negative regulation of immune cell proliferation could be reversed by antisense TGF- β 1 molecules according to the invention, leading to stimulation of immune cell proliferation. In contrast to the molecules according to the invention, antisense molecules chosen conventionally, including that published by Hatzfeld et al. (1991) did not stimulate immune cell proliferation. Even more surprising, several sequences, chosen conventionally, even reduced immune cell proliferation.

Peripheral blood mononuclear cells (PBMCs) were isolated from venous blood of healthy donors by mixing with an equal volume of RPMI 1640 medium (Gibco) supplemented with 10 % fetal calf serum and 1 mM L-glutamine, followed by layering onto Ficoll-Hypaque (Pharmacia) gradients and centrifugation at 400 g for 30 min. PBMCs were removed from the plasma-Ficoll interface and washed in the above medium. Cells (2×10^4 in 100 μ l of medium) were plated into 96 well flat-bottom microtiter plates (Nunc) in serum supplemented complete medium. Cells were activated with 3 μ g/ml phytohemagglutinin and incubated with either no oligodeoxynucleotide (untreated control cells) or with 8 μ M of different antisense phosphorothioate oligodeoxynucleotides, complementary to different regions of the human TGF- β 1 mRNA for 4 days. Cells were then stained with trypan blue to determine cell viability and counted in a Neubauer counting chamber.

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Oligonucleotide sequences were either 33 sequences according to the invention, named sequences TGF- β 1-1 - TGF- β 1-33 or the TGF- β 1 antisense sequence from Hatzfeld et al. (1991), J. Exp. Med., 174, pp. 925 - 929 or 39 other conventionally chosen antisense sequences complementary to human TGF- β 1 mRNA, named N1 - N39 (see figure 3).

Surprisingly the molecules according to the invention were much more effective than antisense TGF- β 1 molecules that were chosen conventionally.

Sequences TGF- β 1-1 - TGF- β 1-33 (see figure 3) enhanced lymphocyte proliferation to between 135 and 213% of untreated controls. In contrast, treatment with the antisense sequence from document Hatzfeld et al. reduced proliferation to 62,8%.

Cells treated with the conventionally chosen TGF- β 1 antisense sequences N1 - N39 surprisingly not only failed to increase lymphocyte proliferation, but several of these sequences even revealed a marked inhibition of cell proliferation to between 51,4% and 77% of controls (sequences N1- N14, N20, N26 and N30 - N39). The antisense TGF- β 1 sequences N15 - N19, N21 - N25, N28 and N29 showed neither significant enhancement nor significant inhibition of cell proliferation with values between 94% and 103%. Sequence N27 showed slight toxicity with a reduction in cell proliferation to 88%.

Inhibition of cell proliferation by some of the TGF- β 1 sequences suggests that they may not be merely ineffective, but also toxic. Analysis of the 26 sequences N1- N14, N20, N26 and N30 - N39 revealed that 23 of them contained either 2 or more sequence motifs with three consecutive Gs (hereafter called GGG motif) or at least one motif with 4, 5, or 6 Gs (motifs GGGG, GGGGG, or GGGGGG). Analysis of the sequence from Hatzfeld et al., which also inhibited PBMC proliferation, surprisingly showed that it too contains a GGGGG plus a GGG motif. The 3 toxic sequences that contained

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neither 2 GGG motifs nor a motif of 4 or more consecutive Gs, i.e. sequences N8, N26, and N35 were found have a base content with 11 - 13 G-bases per sequence.

In contrast to the sequences from Hatzfeld et al., N1- N14, N20, N26 and N30 - N39 the sequences TGF- β 1-1 - TGF- β 1-33 showed a G-content of maximally 6 G-bases, no combination of two GGG motifs within a single sequence and no GGGG, GGGGG or GGGGGG motif. Since the TGF- β 1 mRNA contains more than 85 target regions for a GGG antisense motif and more than 34 target regions for a GGGG antisense motif, this finding in the sequences according to the invention was highly unlikely on a statistical basis.

The non-effective sequences N15 - N19, N21 - N25, N28 and N29 were found to contain a different base content from both the toxic and the effective sequences: They content of the bases A and T taken together (A/T-content) ranged from 14,3% to 28,5%. These sequences neither enhanced nor did they inhibit PBMC proliferation. Thus, they appeared to be neither effective nor toxic. In contrast to these non-effective sequences with an A/T content of 14,3% - 28,5%, the effective sequences TGF- β 1-1 - TGF- β 1-33 were found to have an A/T content of between 33% - 71,4%.

A further difference between the sequences of the invention and two thirds of the other sequences was found with respect to non-specific protein binding: Sequences from document Hatzfeld et al. and N1- N14, N20, N26 and N30 - N39 were found to show markedly enhanced non-specific protein binding compared to the sequences of the invention.

Sequences from Hatzfeld et al. (H) and N1 - N39 are shown in figure 3 as well as TGF- β 1 antisense sequences according to the invention.

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The finding that, while the sequences TGF- β 1-1 - TGF- β 1-33 stimulated proliferation of PBMC immune cells, the sequence from Hatzfeld et al. and sequences N1- N39 where either non-effective with little alteration in PBMC proliferation or had toxic effects and inhibited PBMC proliferation was extended to further antisense sequences both of TGF- β 2 and other genes as detailed in the following examples 2 - 7.

The sequences of the oligonucleotides related with TGF- β 1 are listed in figure 3 for the sake of ease of readability.

For certain applications, including, but not limited to application in dividing cells, including tumor cells, nucleic acid or functional or structural analogs or effective derivatives thereof according to the invention were coupled to folic acid, either at one of the carboxy-groups or at one of the nitrogen atoms of the folic acid.

Furthermore, for certain applications, nucleic acid or functional or structural analogs or effective derivatives thereof according to the invention are mixed with and/or coupled to hormones, steroid hormones such as oestrogen, progesterone, corticosteroids, mineralocorticoids, androgens, phospholipids, peptides, proteoglycans, glycolipids and derivatives therefrom. Preferably, a coupling occurs at R² and/or R³ of figures 1 and 2.

Example 2

p53 antisense nucleic acids (figure 3 shows the respective oligonucleotides)

p53 is a tumor suppressor gene that negatively regulates cell proliferation. Certain mutations in the gene can alter the function of p53 in such a way that it becomes an oncogene. The effects of p53 antisense oligodeoxynucleotides on cells

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containing wild type p53 was analyzed and subsequently also the effect of these sequences on cells with mutated p53.

In cells with wild type p53 effective antisense nucleic acids will lead to downregulation of the wild type p53 protein and thus to enhanced proliferation of the treated cells. Molecules according to the invention are named p53-1 - p53-33. Noneffective p53 antisense sequences were named p53-N-1 - p53-N-18. Toxic sequences, which inhibited proliferation instead of enhancing it as do effective p53 antisense sequences were named p53-T-1 - p53-T-29.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μ M concentration after 2 h.

Two assays to determine cell proliferation were performed:

- To determine 3 H-thymidine incorporation, cells were incubated before harvesting with 0,15 μ Ci 3 H-thymidine/well for 6 h. Cells were lysed by freezing , spotted onto glass filters and the amount of incorporated tritium was determined by liquid scintillation counting.
- To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Surprisingly, only treatment of cells with antisense sequences according to the invention (p53-1 - p53-33) resulted in an increase in thymidine incorporation to between 3- and 9-fold.

In contrast, treatment with noneffective sequences (p53-N-1 - p53-N-18) did not result in significant alterations in thymidine incorporation.

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Furthermore, treatment with toxic antisense p53 sequences (p53-T-1- p53-T-29) resulted in a decrease in proliferation instead of an increase.

In summary, the 33 antisense sequences according to the invention resulted in effective downregulation of negative growth control by p53 and increased cell proliferation, while the 47 other antisense sequences had either no significant effect on cell proliferation or even suppressed cell proliferation.

Example 3

junB antisense nucleic acids (figure 3 shows the respective oligonucleotides)

junB and junD, two genes encoding transcription factors of the jun gene family are negative regulators of cell growth, like p53. The effects of different junB and junD antisense oligodeoxynucleotides was analyzed.

Effective junB and JunD antisense nucleic acids will lead to downregulation of the JunB and JunD proteins respectively and thus to enhanced proliferation of the treated cells. Antisense molecules according to the invention are named JunB-1 - JunB-19 and JunD-1 - JunD-31. Noneffective junB antisense sequences were named JunB-N-1 - JunB-N-57. Toxic sequences, which inhibited proliferation instead of enhancing it were named JunB-T-1 - JunB-T-20 and JunD-T-1 - JunD-T-17.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 µM concentration after 2 h.

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Two assays to determine cell proliferation were performed:

- To determine ^3H -thymidine incorporation, cells were incubated before harvesting with 0,15 μCi ^3H -thymidine/well for 6 h. Cells were lysed by freezing, spotted onto glass filters and the amount of incorporated tritium was determined by liquid scintillation counting.
- To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Surprisingly, again only treatment of cells with antisense sequences according to the invention (JunB-1 - JunB-19 and JunD1- JunD31) resulted in an increase in thymidine incorporation to between 2- and 7-fold.

In contrast, treatment with noneffective sequences (JunB-N-1 - JunB-N-57) did not result in significant alterations in thymidine incorporation.

Furthermore, treatment with toxic antisense junB or JunD sequences (JunB-T-1- JunB-T-20 and JunD-T-1 - JunD-T-17) resulted in a decrease in proliferation instead of an increase.

In summary, the 50 antisense sequences according to the invention resulted in effective downregulation of negative growth control by JunB and JunD , while the 94 other antisense sequences had either no significant effect on cell proliferation or were even toxic.

Example 4 (figure 3 shows the respective oligonucleotides)

erbB-2, is a transmembrane molecule with an intracellular tyrosine kinase activity that is amplified and/or overexpressed by carcinoma cells in a variety of neoplasms including breast cancer, lung cancer, oesophageal and gastric

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cancer, bile duct carcinoma, bladder cancer, pancreatic cancer and ovarian cancer.

In several of these tumors, an amplification and overexpression of the c-erbB-2 gene in the tumor tissue has been shown to correlate with a poor clinical prognosis. Overexpression of p185erbB-2 in non-small-cell lung carcinoma has been shown to impart resistance to a number of chemotherapeutic agents.

Effective erbB-2 antisense nucleic acids will lead to downregulation of the erbB-2 protein and in overexpressing tumor cell lines will lead to reduced cell proliferation of the treated cells. Antisense molecules according to the invention are named erbB-2-1 - erbB-2-83. Noneffective erbB-2 antisense sequences were named erbB-2-N-1 - erbB-2-N-95.

erbB-2 overexpressing SK-Br-3 human mammary carcinoma cells were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 µM concentration after 2 h.

To determine erbB-2 protein expression cells were harvested with a cell scraper and subjected to ELISA protein determination.

Only treatment of cells with antisense sequences according to the invention (erbB-2-1 - erbB-2-83) resulted in a significant reduction in erbB-2 protein expression by 40-95%.

In contrast, treatment with noneffective sequences (erbB-2-N-1 - erbB-2-N-95) did not result in significant alterations in erbB-2 protein expression.

To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

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Only treatment of cells with antisense sequences according to the invention (erbB-2-1 - erbB-2-83) resulted in a reduction in cell number by 35-70%.

In contrast, treatment with noneffective sequences (erbB-2-N-1 - erbB-2-N-95) did not result in significant alterations in cell proliferation.

erbB-2 antisense sequences were shown in figure 3-8 to 3-11

Example 5 (figure 3 shows the respective oligonucleotides)

The c-fos gene encodes an immediate early gene type transcription factor. Effective c-fos antisense nucleic acids will lead to downregulation of the c-Fos protein.

Antisense molecules according to the invention are named c-fos-1 - c-fos-31. Noneffective c-fos antisense sequences were named c-fos-N-1 - c-fos-N-12.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 µM concentration after 2 h.

Expression of the c-Fos protein was determined by ELISA in cell lysates.

Only treatment of cells with antisense sequences according to the invention (c-fos-1 - c-fos-31) resulted in a significant reduction in c-fos protein expression by 45-95%.

In contrast, treatment with noneffective sequences (c-fos-N-1 - c-fos-N-12) did not result in significant alterations in c-Fos protein expression.

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Example 6 (figure 3 shows the respective oligonucleotides)

TGF- β 2, like TGF- β 1 is a member of the transforming growth factor- β family of cytokines.

Overexpression of TGF- β 1 and TGF- β 2 is linked to malignant progression, immunosuppression and escape of the tumors from surveillance by the immune system.

Effective TGF- β 2 antisense nucleic acids will lead to downregulation of the TGF- β 2 growth factor.

Antisense molecules according to the invention are named TGF- β 2-1 - TGF- β 2-38. Noneffective TGF- β 2 antisense sequences were named TGF- β 2-N-1 - TGF- β 2-N-40.

TGF- β 2 overexpressing tumor cells were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 μ M concentration after 2 h.

TGF- β 2 protein expression was determined by ELISA, both in the supernatant and in cell lysates.

Only treatment of cells with antisense sequences according to the invention (TGF- β 2-1 - TGF- β 2-38) resulted in a significant reduction in TGF- β 2 protein expression by 35-80%.

In contrast, treatment with noneffective sequences (TGF- β 2-N-1 - TGF- β 2-N-40) did not result in significant alterations in TGF- β 2 protein expression.

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Example 7 (figure 3 shows the respective oligonucleotides)

rb antisense nucleic acids

rb is a tumor suppressor gene that negatively regulates cell proliferation. The effects of rb antisense oligodeoxynucleotides on cells containing wild type rb was analyzed.

In cells with wild type rb effective antisense nucleic acids will lead to downregulation of the wild type rb protein and thus to enhanced proliferation of the treated cells. Molecules according to the invention are named rb-1 - rb-45. Noneffective rb antisense sequences were named -1 - rb-N-168. Toxic sequences, which inhibited proliferation instead of enhancing it as do effective rb antisense sequences were named rb-T-1- rb-T-16.

Normal human fibroblasts were grown in RPMI medium supplemented with 5% fetal calf serum (FCS) and 2500 cell/well were plated into 96-well microtiter plates. Antisense phosphorothioate oligonucleotides were added at 2 µM concentration after 2 h.

Two assays to determine cell proliferation were performed:

- To determine ^3H -thymidine incorporation, cells were incubated before harvesting with 0,15 µCi ^3H -thymidine/well for 6 h. Cells were lysed by freezing , spotted onto glass filters and the amount of incorporated tritium was determined by liquid scintillation counting.
- To determine cell number, cells were stained with trypan blue and counted in a Neubauer counting chamber.

Surprisingly, only treatment of cells with antisense sequences according to the invention (rb-1 - rb-45) resulted in an increase in thymidine incorporation to between 2- and 6-fold.

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In contrast, treatment with noneffective sequences (rb-N-1 - rb-N-168) did not result in significant alterations in thymidine incorporation.

Furthermore, treatment with toxic antisense rb sequences (rb-T-1- rb-T-16) resulted in a decrease in proliferation instead of an increase.

In summary, the 45 antisense sequences according to the invention resulted in effective downregulation of negative growth control by rb and increased cell proliferation, while the 184 other antisense sequences had either no significant effect on cell proliferation or even suppressed cell proliferation.

Example 8

Oligonucleotide sequences according to the invention were synthesized with various different backbone modifications: Exemplary results are given below.

For the sequence

erbB-2-42: CATCTGGAAACTTCCAGATG

the following chemical modifications were tested in erbB-2 overexpressing carcinoma cells:

1. S-ODN erbB-2-42 (i.e. all backbone linkages were thioate modifications).

C-pS-A-pS-T-pS-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pS-T-pS-G

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2. Me-ODN/S-ODN/Me-ODN erbB-2-42 (i.e. Linkages at the 5' and 3' end were methylphosphonate linkages while linkages in the middle were thioate modifications as follows) :

C-pMe-A-pMe-T-pS-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pMe-T-pMe-G

or

C-pMe-A-pMe-T-pMe-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pMe-A-pMe-T-pMe-G

or

C-pMe-A-pMe-T-pMe-C-pMe-T-pS-G-pS-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pMe-G-pMe-A-pMe-T-pMe-G

or

C-pMe-A-pMe-T-pMe-C-pMe-T-pMe-G-pMe-G-pS-A-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pMe-C-pMe-A-pMe-G-pMe-A-pMe-T-pMe-G

3. Me-ODN / S-ODN erbB-2-42 (i.e. Linkages at the 5' end were methylphosphonate linkages while linkages at the 3' were thioate modifications as follows) :

C-pMe-A-pMe-T-pMe-C-pMe-T-pMe-G-pMe-G-pMe-A-pMe-A-pMe-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pS-T-pS-G

4. S-ODN / Me-ODN erbB-2-42 (i.e. Linkages at the 5' end were methylphosphonate linkages while linkages at the 3' were thioate modifications as follows) :

C-pS-A-pS-T-pS-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-A-pMe-C-pMe-T-pMe-T-pMe-C-pMe-C-pMe-A-pMe-G-pMe-A-pMe-T-pMe-G

5. Me-ODN erbB-2-42 (i.e. linkages methylphosphonate linkages) :

C-pMe-A-pMe-T-pMe-C-pMe-T-pMe-G-pMe-G-pMe-A-pMe-A-pMe-A-C-pMe-T-pMe-T-pMe-C-pMe-C-pMe-A-pMe-G-pMe-A-pMe-T-pMe-G

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6. pN/S-ODN/pN erbB-2-42 (i.e. Linkages at the 5'and 3'end were phosphoramidate linkages while linkages in the middle were thioate modifications as follows):

C-pN-A-pN-T-pS -C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pS-A-pN-T-pN-G

or

C-pN-A-pN-T-pN-C-pS-T-pS-G-pS-G-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pS-G-pN-A-pN-T-pN-G

or

C-pN-A-pN-T-pN-C-pN -T-pS-G-pS-G-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pS-C-pS-A-pN -G-pN-A-pN-T-pN-G

or

C-pN-A-pN-T-pN-C-pN -T-pN -G-pN -G-pS-A-pS-A-pS-C-pS-T-pS-T-pS-C-pN -C-pN-A-pN -G-pN-A-pN-T-pN-G

where

pS stands for substitution of one of the non-bridging oxygen atoms of the backbone linkage with a sulfur atom, while pMe stands for substitution of one of the non-bridging oxygen atoms of the backbone linkage with a methyl group.

pN stands for a N3'->P5' phosphoramidate linkage.

Also a combination of linkages $(N-pS-N-pO-N-pO-N)_n - [pS-N]_m$ wherein n = 1 - 10 and m = 0 - 6 where N stand for any nucleotide or structural or functional analog or derivative thereof.

While the Me-ODN backbone modification strongly reduced the erbB-2 activity of the erbB-2-42 sequence to less than 20%, backbone modifications 1.-4. had strong erbB-2 inhibitory capacity with an inhibition of erbB-2 protein expression by between 78% and 89% at 2 μ M concentration at 48 h after the beginning of treatment of overexpressing carcinoma cells. While the pure S-ODN had the highest suppression capacity with 89%, the Me-ODN/S-ODN/Me-ODN as well as the Me-ODN/S-ODN

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and S-ODN/Me-ODN and pN/S-ODN/pN, displayed reduced protein binding and when tested for complement activation, showed reduced complement activation. These characteristics are advantageous for certain applications e.g. intravenous systemic application in vivo.

Example 9

Similar effects were obtained when testing other sequences according to the invention with the above backbone modifications.

Inhibition of TGF-beta-1 gene expression with the effective sequences for TGF-beta-1 according to the invention was highest with S-ODN and the Me-ODN/S-ODN/Me-ODN backbone modifications and lowest with the Me-ODN modification, while protein binding and complement activation were reduced in sequences containing Me-ODN linkages.

Example 10

Surprisingly, effectivity of sequences according to the invention was significantly improved in various cell types by coupling nucleic acids according to the invention to folic acid:

erbB-2 inhibitory capacity which was relatively low after 24 h compared to 48 h with an inhibition of erbB-2 protein synthesis by 24-37% was markedly increased by coupling sequences according to the invention to folic acid to 48-62% at 2 μ M concentration 24 h after the beginning of treatment of overexpressing carcinoma cells.

Similar effects were achieved by coupling sequences according to the invention to folic acid derivatives including aminopterin and amethopterin.

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Example 11

Surprisingly, effectivity of sequences according to the invention was strongly improved by coupling oligonucleotides according to the invention to cortisol:

Cellular uptake and inhibitory capacity of sequences according to the invention including sequences for TGF-beta-1, TGF-beta-2, c-fos, p53, erbB-2, rb, c-fos, junB, junD, c-jun, MIP-1 alpha, JAK-2, bcl-2 and were markedly increased by coupling cortisol either to the 3' or 5' hydroxyl groups of oligonucleotide sequences according to the invention.

Example 12

Effectivity of sequences according to the invention was also strongly improved in various cell types by coupling nucleic acids according to the invention to or mixing them with other steroid hormones and their derivatives, including oestrogens, anti-oestrogens, prednisone, prednisolone, androgens, anti-androgens, gestagens like progesterone as well as peptides, proteoglycans, glycolipids, phospholipids and derivatives therefrom.

Androgens, particularly androstendion and testosterone, as well as anti-androgens, including cyproteronacetate, flutamide, anandrone, linked to the nucleic acids increased effectiveness of the molecules in various cell types including prostatic carcinoma cells.

Oestrogens, anti-oestrogens and their derivatives, including fosfestrol, toremifene, ethinyloestradiol, diethylstilboestrol and the oestradiol derivatives oestradiol-benzoate, oestradiol-valerinate and oestradiol-undecylate, as well as progesterone and its derivatives, including medroxyprogesteroneacetate and megestrolacetate linked to the oligonucleotides strongly enhanced activity of the molecules according

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to the invention in various cell types including mammary carcinoma cells.

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C l a i m s

1. A method for the preparation of an antisense oligonucleotide or derivative thereof comprising the steps of
 - selecting a target nucleic acid, if necessary elucidating its sequence
 - generating the antisense oligonucleotide with the proviso that
 - the oligonucleotide comprises at least 8 residues,
 - the oligonucleotide comprises at maximum twelve elements, which are capable of forming three hydrogen bonds each to cytosine bases,
 - the oligonucleotide does not contain four or more consecutive elements, capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target molecule or alternatively four or more consecutive elements of GGGG,
 - the oligonucleotide does also not contain 2 or more series of three consecutive elements, capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target molecule, or alternatively 2 or more series of three consecutive elements of GGG, and
 - the ratio between residues forming two hydrogen bonds per residue (2H-bond-R) with the target molecule and those residues forming three hydrogen bonds per residue (3H-bond-R) with the target molecule, is ruled by the following specifications:

$$\frac{3\text{H-bond-R}}{3\text{H-bond-R} + 2\text{H-bond-R}} \geq 0.29$$

- and synthesizing the oligonucleotide thus generated in a per se known manner.

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2. The method according to claim 1, wherein the generated oligonucleotide complies with the following specification

$$\frac{3\text{H-bond-R}}{3\text{H-bond-R} + 2\text{H-bond-R}} = 0.33 \text{ to } 0.86$$

3. The method according to any one of the claims 1 or 2, wherein the generated oligonucleotides are modified for higher nuclease resistance than naturally occurring oligo- or polynucleotides.
4. The method according to claim 3, wherein the generated oligonucleotides are modified at the bases, the sugars or the linkages of the oligonucleotides, preferably by phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.
5. The method according to claim 3 and/or 4, wherein the oligonucleotide has at least two different types of modifications.
6. The method according to any one of the claims 1 to 5, wherein the oligonucleotides are reacted with folic acid, hormones such as steroid hormones or corticosteroides or derivatives thereof by linking the oligonucleotides covalently to or mixing with folic acid, hormones such as steroide hormones or corticosteroides, peptides, proteoglycans, glycolipids or phospholipids.

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7. An antisense oligonucleotide or derivative thereof obtainable according to the method according to any one of the claims 1 to 6 except oligonucleotides represented by Fig. 4.
8. The oligonucleotide or derivative of claim 7, which does not contain four or more consecutive guanosine (N_aGGGN_b) or inosine (N_aIIIIN_b) residues and the oligonucleotide does not contain two or more series of three or more consecutive guanosine residues ($N_aGGGN_cGGGN_b$) and does not contain two ore more series of three or more consecutive inosine residues ($N_aIIIN_cIIIN_b$), wherein N_a , N_b , N_c represent indepently nucleotides or oligonucleotides or derivatives thereof having 0 to 20 residues.
9. The oligonucleotide or derivative of claims 7 and/or 8, comprising a minimum of ten elements and a maximum of 24 elements capable of forming either two or three hydrogen bonds per element.
10. The oligonucleotide or derivative according to any one of the claims 7 to 9, having modifications at the bases, the sugars or the phosphate moieties of the oligonucleotides.
11. The oligonucleotide or derivative of any one of the claims 7 to 10, wherein the modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.

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12. The oligonucleotide or derivative of any one of the claims 7 to 11 coupled to or mixed with folic acid, hormones, steroid hormones such as oestrogene, progesterone, corticosteroids, mineral corticoids, peptides, proteoglycans, glycolipids, phospholipids and derivatives therefrom.
13. The oligonucleotide according to any one of the claims 7 to 12, wherein the antisense oligonucleotide against the TGF- β 1 gene comprise the sequences 41 to 73 of Fig. 3, the oligonucleotides against the gene p53 comprising the sequences 74 to 106 of Fig. 3, the antisense oligonucleotides against junB comprising the sequences 154 to 172 of Fig. 3, the antisense oligonucleotides against junD comprising the sequences 173 to 203 of Fig. 3, the antisense oligonucleotides against the erbB-2 gene comprise the sequences 298 to 380 of Fig 3, the antisense oligonucleotides against c-fos genes comprise the sequences 476 - 506 of Fig. 3; the anti-sense oligonucleotides against the gene TGF- β 2 comprise the sequences 519 to 556 of Fig. 3 as well as the antisense oligonucleotides against the gene rb comprise the sequences 597 to 641 of Fig. 3.; as well as sequences 1273 to 1764. of Fig. 5.
14. A composition comprising an oligonucleotide or derivative according to any one of the claims 7 to 13 for the manufacturing of a medicament or a composition for the inhibition of the genes p53, rb, junD, junB, TGF- β 1, TGF- β 2 to influence cell proliferation, in particular of primary cell cultures such as liver cells, kidney cells, osteoclasts, osteoblasts and/or keratinocytes and/or cells of the blood lineage, such as bone marrow stem cells, and/or progenitor cells of red and white blood cells.

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15. A medicament comprising an oligonucleotide according to any one of the claims 7 to 13 together with additives.
16. The use of the oligonucleotides according to any of the claims 7 to 13 for the preparation of a medicament for the prevention or the treatment of neoplasm, hypoproliferation, hyperproliferation, degenerative diseases, neurodegenerative diseases, ischaemia, disorders of the immune system and/or infectious diseases, and/or metabolic dysfunctions.
17. The use of the oligonucleotides according to any one of the claims 7 to 13 for the analysis of gene function or drug target validation.

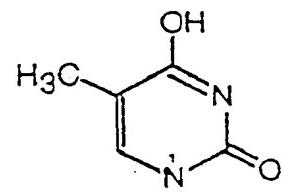
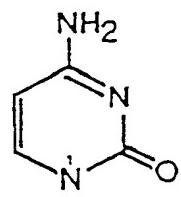
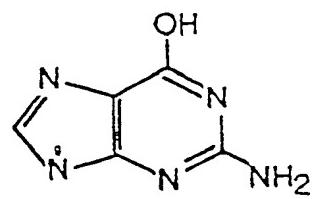
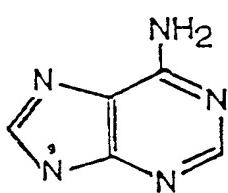
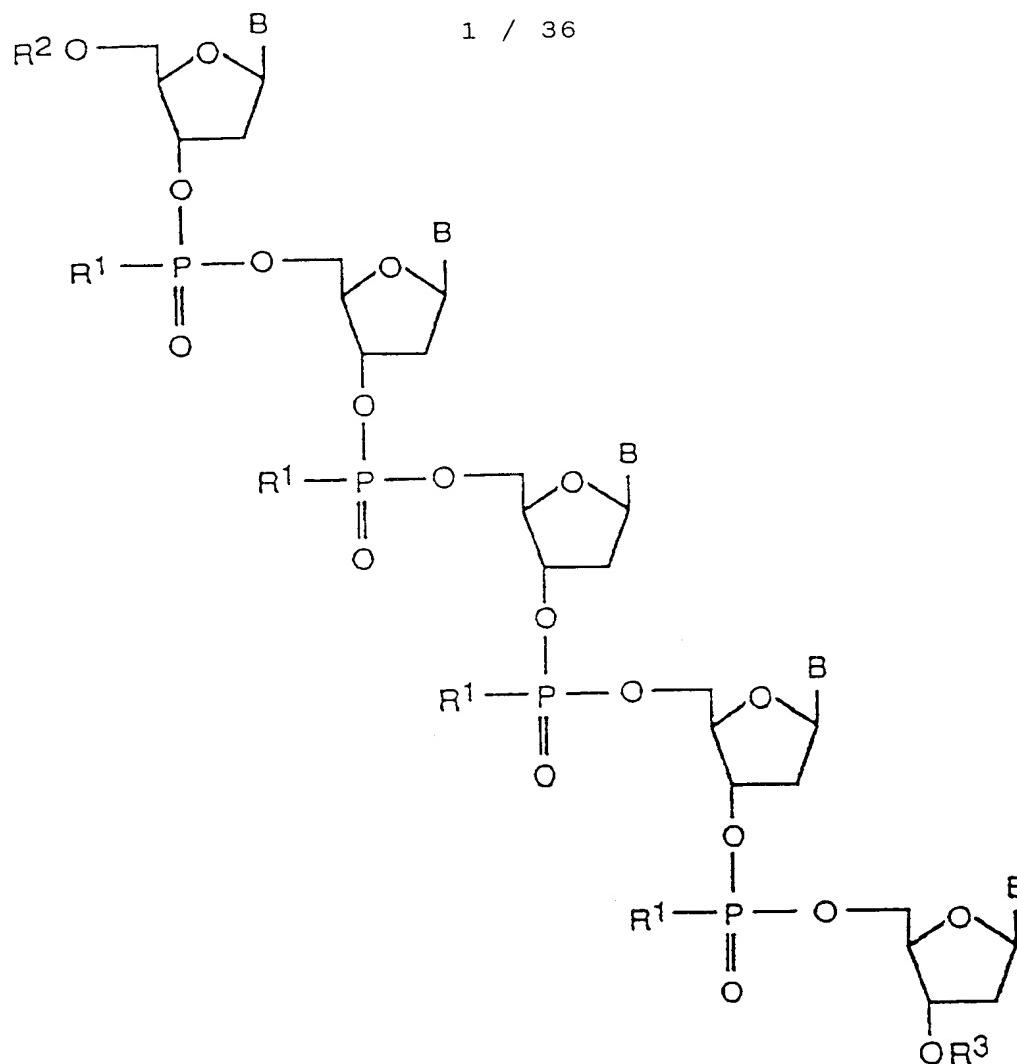
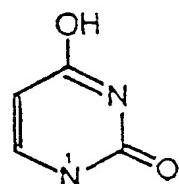
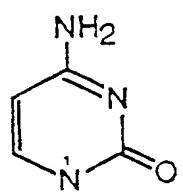
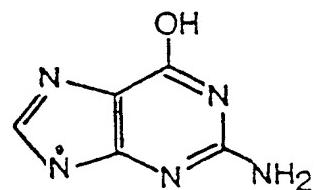
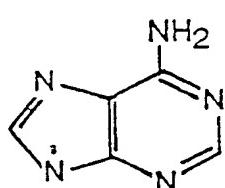
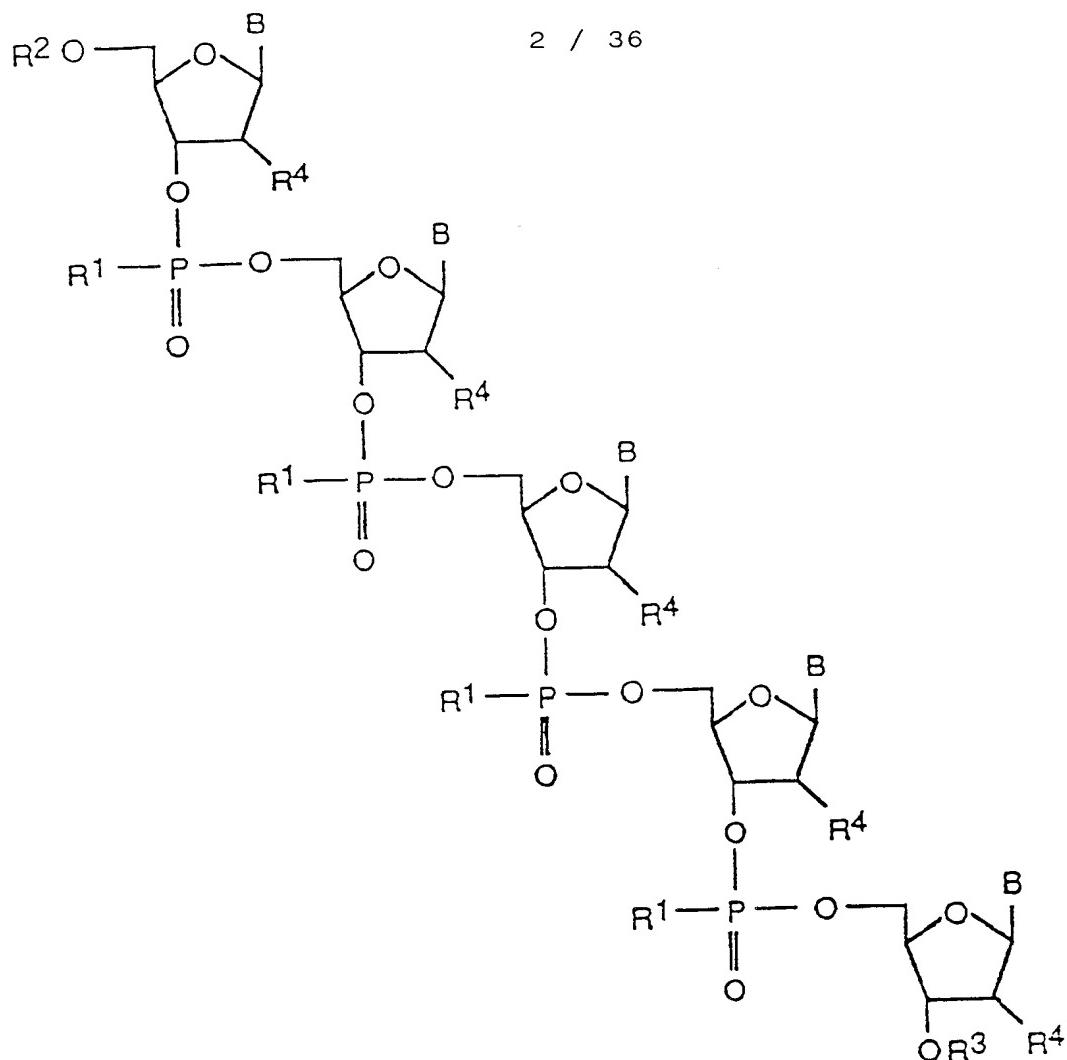


Fig. 1

FIG. 2

1.	A3	CCCGGAGGGCGGCATGGGGA
2.	N1	CCTCAGGGAGAAGGGCGC
3.	N2	GTAAGGAGGGCCTCGAGGG
4.	N3	CTGCAGGGGCTGGGGTC
5.	N4	AGGGCTGGTGTGGGGGG
6.	N5	GGCATGGGGAGGGCGGC
7.	N6	CCGGAGGGCGGCATGGGG
8.	N7	GGGGGGCTGGCGAGGCCG
9.	N8	GGACAGGATCTGGCCGCGGATGG
10.	N9	CCCCCTGGCTCGGGGGGC
11.	N10	GGGCCGGGCGGCACCTCC
12.	N11	GGGCAGGGCGGGCGGC
13.	N12	ACGGCCTCGGGCAGCGGG
14.	N13	GGGTGCTGTTGTACAGGG
15.	N14	GGGTTTCCACCATAGCACGCGG
16.	N15	TCATAGATTCGT
17.	N16	TTGTCACTAGATT
18.	N17	AAGAACATATATATG
19.	N18	AAGAACATATATAT
20.	N19	TTGAAGAACATATATA
21.	N20	CCGGGAGAGCAACACGGG
22.	N21	ACTTTAACTTG
23.	N22	ATTGTTGCTGTATT
24.	N23	ATTGTTGCTGTATT
25.	N24	AATTGTTGCTGTATT
26.	N25	AATTGTTGCTGTAT
27.	N26	GGCGAGTCGCTGGTGCCAGCAGCCGG
28.	N27	GGCGAGTCGCTGG
29.	N28	ACATAAAAGATAA
30.	N29	TGACATAAAAGAT
31.	N30	GGGCCCTCTCCAGCGGGG
32.	N31	GGGCTGGCGGTGCCGGG
33.	N32	GGGGCAGGGCCCAGGCA
34.	N33	GGCTCAAATGTAGGGGC
35.	N34	CGGGTTATGCTGGTTACAGGGC
36.	N35	CGGCGCCGCCGAGGCAGCCGG
37.	N36	GGGGCGGGCGGGGACC
38.	N37	GGGCGGGGCGGGGGCGGGG
39.	N38	GGGCAGGGTGGGGCGGGG
40.	N39	GGCAAGGCAGCGGGCGGGG
41.	TGF-β1-1	CGGTAGCAGCAGCG
42.	TGF-β1-2	CCAGTAGCCACAGC
43.	TGF-β1-3	GCAGGTGGATAGTCC
44.	TGF-β1-4	CTTGCAGGTGGATAG
45.	TGF-β1-5	CGATAGCTTGCAAGG
46.	TGF-β1-6	CCATGTCGATAGCTTGC
47.	TGF-β1-7	CTCGATGCGCTTCG
48.	TGF-β1-8	CCTCGATGCGCTTCC
49.	TGF-β1-9	GGATGGCCTCGATGC
50.	TGF-β1-10	GGACAGGATCTGGCC
51.	TGF-β1-11	CGCAGCTTGGACAGG
52.	TGF-β1-12	GAGCCGCAGCTTGG
53.	TGF-β1-13	CGAGCCGCAGCTTGG
54.	TGF-β1-14	ACCTCCCCCTGGCT
55.	TGF-β1-15	CCACCATTAGCAGC
56.	TGF-β1-16	GAACTTGTCATAGATTTC
57.	TGF-β1-17	GCTGTGTACTCTGC
58.	TGF-β1-18	GCTCCACGTGCTGC
59.	TGF-β1-19	GAATTGTTGCTGTATTTC
60.	TGF-β1-20	GCCAGGAATTGTTGC
61.	TGF-β1-21	GTGACATAAAAGATAAC
62.	TGF-β1-22	GGCTCAACCACTGCC
63.	TGF-β1-23	GCTGTACAGGAGC
64.	TGF-β1-24	CCTGCTGTCACAGG
65.	TGF-β1-25	GCAGTGTGTTATCCCTGC
66.	TGF-β1-26	GCAGTGTGTTATCCC

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67.	TGF-β1-27	CCAGGTCAACCTCGG
68.	TGF-β1-28	GCCATGAATGGTGGC
69.	TGF-β1-29	GCCATGAATGGTGG
70.	TGF-β1-30	CCATGAGAAGCAGG
71.	TGF-β1-31	GGAAGTCAATGTACAGC
72.	TGF-β1-32	CCACGTAGTACACGATGG
73.	TGF-β1-33	GCACATTGCAGGAGC
74.	p53-1	CCATGGCAGTGACC
75.	p53-2	GGCTCCTCCATGGC
76.	p53-3	GCTAGGATCTGACTGC
77.	p53-4	CCTGACTCAGAGGG
78.	p53-5	GGTCTGAAAATGTTTCC
79.	p53-6	CCATTGCTTGGGACGG
80.	p53-7	GCATCAAATCATCC
81.	p53-8	CCATTGTTCAATATCG
82.	p53-9	GGTCTTCAGTGAACC
83.	p53-10	GGAGCTTCATCTGGACC
84.	p53-11	CCTCTGGCATTCTGG
85.	p53-12	AGGGACAGAACGATG
86.	p53-13	GTTTTCTGGGAAGG
87.	p53-14	GGTTTTCTGGGAAG
88.	p53-15	AGGTTTTCTGGGAAG
89.	p53-16	GTAGGTTTCTGGG
90.	p53-17	GGTAGGTTTCTGG
91.	p53-18	CCAGAAATGCAAGAACGCC
92.	p53-19	GCTGTCCCAGAACATGC
93.	p53-20	GCAAGTCACAGAACATTGGC
94.	p53-21	CCACAGCTGCACAGG
95.	p53-22	GGTGTGGAATCAACC
96.	p53-23	GTCATGTGCTGTGA
97.	p53-24	CGCTATCTGAGCAGCG
98.	p53-25	CCAGTGTGATGATGG
99.	p53-26	CCAGTAGATTACCACTGG
100.	p53-27	GGCACAAACACGCACC
101.	p53-28	CCACGGATCTGAAGG
102.	p53-29	CGGAACATCTCGAACGCG
103.	p53-30	CCTCATTTCAGCTCTCGG
104.	p53-31	CCTTGAGTTCCAAGG
105.	p53-32	CCTTTTTGGACTTCAGG
106.	p53-33	GGAGGTAGACTGACCC
107.	p53-N-1	AAAAATGTTTCCT
108.	p53-N-2	TGAAAATGTTTC
109.	p53-N-3	CTGAAAATGTT
110.	p53-N-4	TCTGAAAATGTT
111.	p53-N-5	TCTGAAAATGTT
112.	p53-N-6	AAATCATCCATT
113.	p53-N-7	TTGTTCAATATC
114.	p53-N-8	ATTGTTCAATATC
115.	p53-N-9	ATTGTTCAATAT
116.	p53-N-10	CATTGTTCAATAT
117.	p53-N-11	CATTGTTCAATA
118.	p53-N-12	AAAAGTGTTCCT
119.	p53-N-13	ACATGAGTTTTTAT
120.	p53-N-14	AACATGAGTTTTTAT
121.	p53-N-15	ACATGAGTTTTTA
122.	p53-N-16	AACATGAGTTTTTA
123.	p53-N-17	AACATGAGTTTTT
124.	p53-N-18	AAAACATCTTGT
125.	p53-T-1	CAGAGGGGGCTCGACGC
126.	p53-T-2	CTGACTCAGAGGGGCTC
127.	p53-T-3	AGGGGGACAGAACG
128.	p53-T-4	TTGGGACGGCAAGGGGACAGAA
129.	p53-T-5	TGGGACGGCAAGGGGGA

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130.	p53-T-6	GCCACGGGGGGAGCA
131.	p53-T-7	GCAGGGGCCACGGGGGAG
132.	p53-T-8	AGGGGGCACGGGG
133.	p53-T-9	CAGGGGCCACGGGG
134.	p53-T-10	GGTGCAGGGGCCACG
135.	p53-T-11	TGGTGCAAGGGCCGCCGG
136.	p53-T-12	GGGGCTGGTGCAGGGGCC
137.	p53-T-13	AGGGGGCTGGTGCAGGGG
138.	p53-T-14	GGGCTGGTGCAGGG
139.	p53-T-15	GAGGGGGCTGGTGCAG
140.	p53-T-16	AGGAGGGGGCTGGTG
141.	p53-T-17	GGGCCAGGAGGGGGCTGG
142.	p53-T-18	AGGGGCCAGGAGGGGGCT
143.	p53-T-19	GGGGCCAGGAGGGG
144.	p53-T-20	CAGGGGCCAGGAGGG
145.	p53-T-21	TCTGGGAAGGGACAGA
146.	p53-T-22	TGAGGGCAGGGGAGTA
147.	p53-T-23	TTGAGGGCAGGGGAG
148.	p53-T-24	CGGGTGCAGGGCGGGGTG
149.	p53-T-25	CGGACCGGGTGCAGGGCGGGGT
150.	p53-T-26	CGGGTGCAGGGCGGG
151.	p53-T-27	GGACGCGGGTGCAGGGCG
152.	p53-T-28	TGGGGCAGCGCCTACAC
153.	p53-T-29	GGTGGGGCAGCGCCT
154.	JunB-1	CCATTTAGTGCACATCCGG
155.	JunB-2	CCATTTAGTGCACATCC
156.	JunB-3	GCTGTTCCATTAGTGC
157.	JunB-4	GTAGTCGTGTAGAG
158.	JunB-5	GTTTGTAGTCGTGTAG
159.	JunB-6	GTTTCAGGAGTTGTAG
160.	JunB-7	CCAGCTCGAAGAGG
161.	JunB-8	CGTCGTCGTGATCACG
162.	JunB-9	GGTAAAAGTACTGTCC
163.	JunB-10	GGCTTACAAAGCC
164.	JunB-11	CTTGTGCAGATCGTCAG
165.	JunB-12	CGTGGTTCATCTGTGC
166.	JunB-13	CACGTGGTTCATCTGTG
167.	JunB-14	CCTCCTGAAGGTGG
168.	JunB-15	CGCTCCACTTGATGCG
169.	JunB-16	CCTTGTCCCTCCAGG
170.	JunB-17	GGTACTCGACAGCC
171.	JunB-18	CTGACGTGGTCATG
172.	JunB-19	CCGTTGCTGACGTGG
173.	JunD-1	CATCCTCCGCCTCC
174.	JunD-2	GTTTCCATCCTCCG
175.	JunD-3	GGTGTTCATCCCTCC
176.	JunD-4	GGTGTTCATCCCTC
177.	JunD-5	GCTCAGCGCCTCATC
178.	JunD-6	CCTTCTTCATCATGCTGC
179.	JunD-7	CCTTCTTCATCATGCTG
180.	JunD-8	CCTTCTTCATCATGC
181.	JunD-9	GCGTCCTTCATCATGC
182.	JunD-10	CCTGCTCACTCAGG
183.	JunD-11	CGCAGGCTTGAGCG
184.	JunD-12	GCCAGCTTCAGCAGC
185.	JunD-13	GGTGGTGACCAGCC
186.	JunD-14	CCTCGGCGAACTCC
187.	JunD-15	GCTTGTGAAATCC
188.	JunD-16	GGTTCTGCTTGAAATCC
189.	JunD-17	GCTGCTCAGGTTCGC
190.	JunD-18	GAAGGCGACCGTC
191.	JunD-19	CGAAGGCGACCGTC
192.	JunD-20	GCACCGTCAGGGC
193.	JunD-21	CGTGTCCATGTCGATGG
194.	JunD-22	CGTGTCCATGTCGATG

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195.	JunD-23	GCGTGTCCATGTGCG
196.	JunD-24	CCAGCTTGCCTTGCG
197.	JunD-25	CGCTCCAGCTTGCG
198.	JunD-26	CGTGTTCAGACTCTTGAG
199.	JunD-27	CGTGTTCAGCTCTTG
200.	JunD-28	GCTGTTGACGTGGC
201.	JunD-29	CGACTCAGTACGCC
202.	JunD-30	GCCATGCCGACTC
203.	JunD-31	CCCTTGGAGGTGGC
204.	JunB-N-1	TTTTAGTGCACAT
205.	JunB-N-2	TGTTCCATTAGT
206.	JunB-N-3	AAAAAAAGTGGAAAG
207.	JunB-N-4	TACAAAAAAAAGTG
208.	JunB-N-5	ATACAAAAAAAAGT
209.	JunB-N-6	CATACAAAAAAAAGT
210.	JunB-N-7	CATACAAAAAAAAG
211.	JunB-N-8	GAAAAAAAACATAC
212.	JunB-N-9	CAGAAAAAAAACATAC
213.	JunB-N-10	CAGAAAAAAAACAT
214.	JunB-N-11	TTCAATATGAATCG
215.	JunB-N-12	TATTCAATATGAATCG
216.	JunB-N-13	TATTCAATATGAATC
217.	JunB-N-14	TATTCAATATGAAT
218.	JunB-N-15	TATATTCAATATGAA
219.	JunB-N-16	TTATATTCAATATGA
220.	JunB-N-17	TATTATAATTCAATATGA
221.	JunB-N-18	TTATATTCAATATG
222.	JunB-N-19	TATTATATTCAATATG
223.	JunB-N-20	ATTATATTCAATAT
224.	JunB-N-21	TATTATATTCAATAT
225.	JunB-N-22	ATATATTATATTCAATAT
226.	JunB-N-23	AAATATATTATATTCAATAT
227.	JunB-N-24	TATTATATTCAATA
228.	JunB-N-25	ATATATTATATTCAATA
229.	JunB-N-26	CAAATATATTATATTCAATA
230.	JunB-N-27	TATATTATATTCAAT
231.	JunB-N-28	AATATATTATATTCAAT
232.	JunB-N-29	TATATTATATTCAA
233.	JunB-N-30	CAAATATATTATATTCAA
234.	JunB-N-31	CAAATATATTATATTCA
235.	JunB-N-32	CAAATATATTATATTCA
236.	JunB-N-33	CACAAATATATTATATT
237.	JunB-N-34	AAATATATTATATT
238.	JunB-N-35	CAAATATATTATATT
239.	JunB-N-36	CAAATATATTATATT
240.	JunB-N-37	CACAAATATATTATATT
241.	JunB-N-38	CACAAATATATTAT
242.	JunB-N-39	TACACAAATATATTAT
243.	JunB-N-40	TACACAAATATATTA
244.	JunB-N-41	TAAATACACAAATATATT
245.	JunB-N-42	AATACACAAATATA
246.	JunB-N-43	GTAAATACACAAATA
247.	JunB-N-44	TGTTAAATACACAA
248.	JunB-N-45	TTTAGAGACTAAGT
249.	JunB-N-46	ATAAACTCTTTAGA
250.	JunB-N-47	TAATATAAACTCTTTAG
251.	JunB-N-48	TAATATAAACTCTTTA
252.	JunB-N-49	TTAAAAATAAACTCTTT
253.	JunB-N-50	CTTAAATAAAACTC
254.	JunB-N-51	TAATAGAACAAACA
255.	JunB-N-52	TAATAGAACAAAC
256.	JunB-N-53	CAATAAAAGAACAA
257.	JunB-N-54	TCAATAAAAGAACAA
258.	JunB-N-55	TCAATAAAAAGAAC
259.	JunB-N-56	TTCAATAAAAAGAA
260.	JunB-N-57	TAGATTCAATAAAAAGA

261.	JunB-T-1	TGGCGCGGGCGGGTAGC
262.	JunB-T-2	GGGCTGGCGCGGGCGGGTAG
263.	JunB-T-3	TCGGGGCTGGCGCGGGCGGG
264.	JunB-T-4	TGGGTCCCTGGTCGCCGTTCTCGGG
265.	JunB-T-5	AGGGTCCCTGCAGGGCGG
266.	JunB-T-6	GGGAGGGTCCCTGCAGGG
267.	JunB-T-7	GGGAGGGTCCCTGCAGGG
268.	JunB-T-8	TGGGCCGGGTCCGC
269.	JunB-T-9	TCCCAGGGGTGTAG
270.	JunB-T-10	AGTACTGTCCCAGGGGTGT
271.	JunB-T-11	GGGACACGTTGGGGGTG
272.	JunB-T-12	GCCGGGGGGCCCCCGGTAGC
273.	JunB-T-13	CGGGCCCAGCCGGGGC
274.	JunB-T-14	CGGGCCCAGCCGGG
275.	JunB-T-15	GGGAGGTGGCTCCGGCGG
276.	JunB-T-16	AGGGCGCGCGTGTGGGA
277.	JunB-T-17	GGGTGGCCACCAGCGAAGGG
278.	JunB-T-18	AGGGGCAGGGGACGT
279.	JunB-T-19	TAAAGGGCAGGGGACGT
280.	JunB-T-20	AGGGGGTGTCCGTAAAGGGG
281.	JunD-T-1	GGGGACCGGAACGTGCCGCC
282.	JunD-T-2	CGGGGAACAAGCGGCCGGGG
283.	JunD-T-3	GGCGTCTGGGGCG
284.	JunD-T-4	GCAGCCGTCGGGGGC
285.	JunD-T-5	AGGGGGTAGGAGGGCGGG
286.	JunD-T-6	GCGCTGGGGCGCC
287.	JunD-T-7	GGCGTCTGGGGGGT
288.	JunD-T-8	GGGGAGGCCAGCTC
289.	JunD-T-9	GGCGGCCACCTTGGGG
290.	JunD-T-10	GCGGCCGCCGCCGGGG
291.	JunD-T-11	GGGCGCGGCCGCCGGGG
292.	JunD-T-12	GGGGTGGCGGGCGGG
293.	JunD-T-13	GGGGGTGGCGGGCGGC
294.	JunD-T-14	TGGGGCAGCAGCTGGCAG
295.	JunD-T-15	CGGGGGCGCCACGACACC
296.	JunD-T-16	CGGGGGCGCCACGACAC
297.	JunD-T-17	GGGCCGCACCCCTCTCCAAGTCCGGGG
298.	ErbB-2-1	GCAGCAGTCAGTGG
299.	ErbB-2-2	CCATTGTCAGCACGG
300.	ErbB-2-3	GGTCTCCATTGTCAGC
301.	ErbB-2-4	GGTGGTATTGTTCAAGC
302.	ErbB-2-5	GCTGGATCAAGACCC
303.	ErbB-2-6	CCACAAAATCGTGTCC
304.	ErbB-2-7	CCTTCCACAAAATCGTGTCC
305.	ErbB-2-8	GGTTGTTCTTGTGG
306.	ErbB-2-9	CCTCTTGGTTGTGC
307.	ErbB-2-10	CCAGAGTCTCAAACACTTGG
308.	ErbB-2-11	GGTAACCTGTGATCTCTTCC
309.	ErbB-2-12	CCTGCAGTACTCGG
310.	ErbB-2-13	GGCATTACATACTCC
311.	ErbB-2-14	GCAAACAGTGCCTGGC
312.	ErbB-2-15	CGCATCGTGTACTTCCG
313.	ErbB-2-16	GCACGTTCCGAGCG
314.	ErbB-2-17	GGTACCAAGATACTCC
315.	ErbB-2-18	CCAGTGGAGACCTGG
316.	ErbB-2-19	CCTGAGGACACATCAGG
317.	ErbB-2-20	CCTCACCTGGTTGTGAGC
318.	ErbB-2-21	GGAAGATGTCCTTCC
319.	ErbB-2-22	GCACACTGCTCATGGC
320.	ErbB-2-23	GCTGTCACCTCTGG
321.	ErbB-2-24	CCTCTGCTGTCAACC
322.	ErbB-2-25	CCACACATCACTCTGG
323.	ErbB-2-26	CCTCCTCTTCAGAGG

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324.	ErbB-2-27	CCTTCTGGTTCACACTGG
325.	ErbB-2-28	CATGGTGCTCACTGCG
326.	ErbB-2-29	CTTGGTTGTGAGCG
327.	ErbB-2-30	GGACAGGCAGTCAC
328.	ErbB-2-31	GTCACCTCTTGGTTGTGC
329.	ErbB-2-32	CCAGAGTCTCAAACAC
330.	ErbB-2-33	CACATACTCCCTGG
331.	ErbB-2-34	GACCAGCACGTTCCG
332.	ErbB-2-35	GTTGGTGTCTATCAGTG
333.	ErbB-2-36	CCCTGGTAGAGGTG
334.	ErbB-2-37	CTCAAACACTTGGAGC
335.	ErbB-2-38	CACACATCACTCTGGTGG
336.	ErbB-2-39	GCACAGACAGTGCGC
337.	ErbB-2-40	CATGGCAGCAGTCAG
338.	ErbB-2-41	CTGCTCATGGCAGCAG
339.	ErbB-2-42	CATCTGGAAACTTCCAGATG
340.	ErbB-2-43	CTGGAAACTTCCAG
341.	ErbB-2-44	CATAACTCCACACATCACTC
342.	ErbB-2-45	CACCATTAACCTCACACATC
343.	ErbB-2-46	CTGGTGGGTGAACC
344.	ErbB-2-47	CGGATTACTGCAGG
345.	ErbB-2-48	CGCTAGGTGTCAGCG
346.	ErbB-2-49	GCCATCACGTATGC
347.	ErbB-2-50	GCATACACCAGTCAGC
348.	ErbB-2-51	CCATCAAATACATCGG
349.	ErbB-2-52	CCAGCAGAAGTCAGG
350.	ErbB-2-53	GCTTCATGTCTGTGC
351.	ErbB-2-54	GGTGAGTTCCAGGTTCC
352.	ErbB-2-55	CCACAAAATCGTGTCTGG
353.	ErbB-2-56	CCCTTACACATCGG
354.	ErbB-2-57	GCAGCTCACAGATGC
355.	ErbB-2-58	GCACTGGTAACTGC
356.	ErbB-2-59	CCTGGATATTGGCACTGG
357.	ErbB-2-60	CCAGCAAACCTCTGG
358.	ErbB-2-61	GCAGAAATGCCAGGC
359.	ErbB-2-62	CCATTGTGCAGAAATTG
360.	ErbB-2-63	CCCTGCAGTACTCGG
361.	ErbB-2-64	GGCATTACACATACTCCC
362.	ErbB-2-65	GGTCAGGTTTCACACC
363.	ErbB-2-66	CCAGGTCCACACAGG
364.	ErbB-2-67	CCTTGTCATCCAGG
365.	ErbB-2-68	GGATCCCAAAGACC
366.	ErbB-2-69	CCTCAACACTTTGATGG
367.	ErbB-2-70	GCTGTGTCACCAGC
368.	ErbB-2-71	GGTCTAACAGGGCAGCC
369.	ErbB-2-72	GGCAATCTGCATACACC
370.	ErbB-2-73	CCTGTGTACGAGCC
371.	ErbB-2-74	CCATCCACTTGATGG
372.	ErbB-2-75	CCCACACAGTCACACC
373.	ErbB-2-76	CCATCGTAAGGTTGG
374.	ErbB-2-77	CCTTTTCCAGCAGG
375.	ErbB-2-78	GGAGAACATTGAGACACC
376.	ErbB-2-79	CCAAGTCCTCATTCTGG
377.	ErbB-2-80	CCATCAGTCTCAGAGG
378.	ErbB-2-81	CCTTGAAGGTGCTGG
379.	ErbB-2-82	GGCATGGCAGGTTCC
380.	ErbB-2-83	CCTGGCATGGCAGG
381.	ErbB-2-N-1	AGATGTATAGGTAA
382.	ErbB-2-N-2	ATTTTCACATTCTC
383.	ErbB-2-N-3	AATTTTCACATTCTC
384.	ErbB-2-N-4	AATTTTCACATTCT
385.	ErbB-2-N-5	GAATTTTCACATT
386.	ErbB-2-N-6	GGAATTTTCACATT
387.	ErbB-2-N-7	AGATTCTTTGTTG
388.	ErbB-2-N-8	AAGATTCTTTGTTG
389.	ErbB-2-N-9	AAGATTCTTTGTT

390.	ErbB-2-N-10	TAAGATTTCTTGT
391.	ErbB-2-N-11	CTAAGATTTCTTGT
392.	ErbB-2-N-12	TAAGATTTCTTGT
393.	ErbB-2-N-13	CTAAGATTTCTTGT
394.	ErbB-2-N-14	CTAAGATTTCTTGT
395.	ErbB-2-N-15	TCTAAGATTTCTT
396.	ErbB-2-N-16	GTCTAAGATTTCTT
397.	ErbB-2-N-17	GTCTAAGATTTCTT
398.	ErbB-2-N-18	TTCGTCTAAGATT
399.	ErbB-2-N-19	ATTTTGACATGGTT
400.	ErbB-2-N-20	AATTTTGACATGGTT
401.	ErbB-2-N-21	AATTTTGACATGGT
402.	ErbB-2-N-21	TAATTTGACATGGT
403.	ErbB-2-N-23	TAATTTGACATGG
404.	ErbB-2-N-24	GTAATTTGACATG
405.	ErbB-2-N-25	TGTAATTTGACATG
406.	ErbB-2-N-26	TGTAATTTGACAT
407.	ErbB-2-N-27	TCTGTAATTTGACAT
408.	ErbB-2-N-28	CTGTAATTTGACA
409.	ErbB-2-N-29	TCTGTAATTTGACA
410.	ErbB-2-N-30	TCTGTAATTTGAC
411.	ErbB-2-N-31	GTCTGTAATTTGA
412.	ErbB-2-N-32	AAGTCTGTAATTTGA
413.	ErbB-2-N-33	AGTCTGTAATTTG
414.	ErbB-2-N-34	AAGTCTGTAATTTG
415.	ErbB-2-N-35	AAGTCTGTAATTT
416.	ErbB-2-N-36	GAAGTCTGTAATTT
417.	ErbB-2-N-37	GAAGTCTGTAATTT
418.	ErbB-2-N-38	ATGTAGACATCAAT
419.	ErbB-2-N-39	ATCATCCAACATT
420.	ErbB-2-N-40	AATCATCCAACATT
421.	ErbB-2-N-41	AATCATCCAACATT
422.	ErbB-2-N-42	ACCATCAAATACAT
423.	ErbB-2-N-43	AAAAACGTCCTTGA
424.	ErbB-2-N-44	TTTTGTTCTTAGACA
425.	ErbB-2-N-45	TTTTGTTCTTAGAC
426.	ErbB-2-N-46	TAAACAGAAAAGCA
427.	ErbB-2-N-47	ACTAAACAGAAAAG
428.	ErbB-2-N-48	AAACTAAACAGAAAAG
429.	ErbB-2-N-49	AACTAAACAGAAA
430.	ErbB-2-N-50	AAACTAAACAGAAA
431.	ErbB-2-N-51	AAACTAAACAGAAA
432.	ErbB-2-N-52	TAAAAACTAACAGAAA
433.	ErbB-2-N-53	AAAAACTAAACAGAA
434.	ErbB-2-N-54	GTAAAAACTAACAGAA
435.	ErbB-2-N-55	AAAAACTAAACAGA
436.	ErbB-2-N-56	TAAAAACTAACAGA
437.	ErbB-2-N-57	TAAAAACTAACAG
438.	ErbB-2-N-58	GTAAAAACTAAACA
439.	ErbB-2-N-59	AAAAAGTAAAAACTAAACA
440.	ErbB-2-N-60	AGTAAAAACTAAC
441.	ErbB-2-N-61	AAAAAAAGTAAAAC
442.	ErbB-2-N-62	AAGTAAAAACTAAA
443.	ErbB-2-N-63	AAAAAAAGTAAAAC
444.	ErbB-2-N-64	AAAGTAAAAACTAA
445.	ErbB-2-N-65	AAAAGTAAAAACTA
446.	ErbB-2-N-66	AAAAAAAGTAAAAC
447.	ErbB-2-N-67	AAAAAGTAAAAC
448.	ErbB-2-N-68	AAAAAAAGTAAAAC
449.	ErbB-2-N-69	AAAAAAAGTAAAAC
450.	ErbB-2-N-70	CAAAAAAGTAAAAC
451.	ErbB-2-N-71	AAAAAAAGTAAAAA
452.	ErbB-2-N-72	CAAAAAAGTAAAAA
453.	ErbB-2-N-73	AACAAAACAAAAAAAGTAAA
454.	ErbB-2-N-74	AAACAAAAAAAGTA
455.	ErbB-2-N-75	CAAAACAAAAAAAGTA
456.	ErbB-2-N-76	CAAAACAAAAAAAGT

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457.	ErbB-2-N-77	CAAAACAAAAAAAG
458.	ErbB-2-N-78	CTTTAAAAAAACAAAAC
459.	ErbB-2-N-79	TCTTTAAAAAAACAAA
460.	ErbB-2-N-80	GTCTTAAAAAAACAAA
461.	ErbB-2-N-81	GTCTTAAAAAAACA
462.	ErbB-2-N-82	GTCTTAAAAAAAC
463.	ErbB-2-N-83	TTTATTCGTCCTT
464.	ErbB-2-N-84	TCTTTATTCGTCCT
465.	ErbB-2-N-85	TATTTGCAAATGGA
466.	ErbB-2-N-86	TATATTGCAAATGG
467.	ErbB-2-N-87	TATATTGCAAATG
468.	ErbB-2-N-88	CAAAATATATTCGCAAATG
469.	ErbB-2-N-89	CAAAATATATTCGCAAAT
470.	ErbB-2-N-90	CAAAATATATTCGCA
471.	ErbB-2-N-91	CAAAATATATTCG
472.	ErbB-2-N-92	TTCCAAAATATATTG
473.	ErbB-2-N-93	TTTCCAAAATATATT
474.	ErbB-2-N-94	GTTTCCAAAATATATT
475.	ErbB-2-N-95	GTTTCCAAAATAT
476.	c-fos-1	GGTTAGGCAAAGCC
477.	c-fos-2	CCGAGAACATCATCGTGG
478.	c-fos-3	CCGAGAACATCATCGTG
479.	c-fos-4	CCGAGAACATCATCG
480.	c-fos-5	CGTAGCTCGCGTTGAAGC
481.	c-fos-6	CCATGCTGGAGAAGG
482.	c-fos-7	CCGTGCAGAAGTCC
483.	c-fos-8	GGAATGAAGTTGGC
484.	c-fos-8	TGACCGTGGGAATG
485.	c-fos-10	TGGCAGTGACCGTG
486.	c-fos-11	AGATGGCAGTGACC
487.	c-fos-12	CGAGATGGCAGTGACC
488.	c-fos-13	CCAGCCACTGCAGG
489.	c-fos-14	GCACCAGCCACTGC
490.	c-fos-15	CCCTGGAGTAAGCC
491.	c-fos-16	GGAGATAACTGTTCCACC
492.	c-fos-17	GGAGATAACTGTTCC
493.	c-fos-18	CTTCTAGTTGGCTCG
494.	c-fos-19	CATCTTCTAGTTGG
495.	c-fos-20	TCTCATCTTCTAGTTGG
496.	c-fos-21	CTGCAAAGCAGACTTCTC
497.	c-fos-22	CCTTCAGCAGGTTGG
498.	c-fos-23	CCCAGGTCACTCAGG
499.	c-fos-24	CCAGTCAGATCAAGG
500.	c-fos-25	GGTGAAGGCCTCCTC
501.	c-fos-26	CAGGGTGAAGGCCTC
502.	c-fos-27	CCTGGATGATGCTGG
503.	c-fos-28	CCACTGTGCAGAGG
504.	c-fos-29	GGAGTACAGGTGACC
505.	c-fos-30	GCTCATTGCTGCTGC
506.	c-fos-31	GGAAGGCTCATTGCTGC
507.	c-fos-N-1	TTTTCTCTTCTTCT
508.	c-fos-N-2	ATCTTATTCTTCTTC
509.	c-fos-N-3	CATCTTATTCTTCTT
510.	c-fos-N-4	TAGTTTTCTTCTTCT
511.	c-fos-N-5	TCTAGTTTTCTTCTT
512.	c-fos-N-6	AACTCTAGTTTTTC
513.	c-fos-N-7	GAACCTCTAGTTTT
514.	c-fos-N-8	TGAACCTCTAGTTTT
515.	c-fos-N-9	ATGAACCTCTAGTTTT
516.	c-fos-N-10	TGAACCTCTAGTTTT
517.	c-fos-N-11	ATGAACCTCTAGTTTT
518.	c-fos-N-12	ATGAACCTCTAGTTT
519.	TGF- β 2-1	GCACACAGTAGTGC

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520.	TGF-β2-2	GCAGGATCAGAAAAGC
521.	TGF-β2-3	GCAGGTAGACAGGC
522.	TGF-β2-4	GCTTGCTCAGGATCTGC
523.	TGF-β2-5	GCAAGTCCCCTGGTGC
524.	TGF-β2-6	CCTGGAGCAAGTCC
525.	TGF-β2-7	CGTAGTACTCTCGTCG
526.	TGF-β2-8	CGTAGTACTCTTCG
527.	TGF-β2-9	GTAAACCTCCTTGG
528.	TGF-β2-10	GTCTATTGTAACCTCC
529.	TGF-β2-11	GCATGTCATTGTAACCC
530.	TGF-β2-12	GGCATCAAGGTACCC
531.	TGF-β2-13	GGCATCAAGGTACC
532.	TGF-β2-14	GCTTCACCAAATTGGAAGC
533.	TGF-β2-15	GAGAACCTGATATAGCTC
534.	TGF-β2-16	GGAGATGTTAAATCTTGG
535.	TGF-β2-17	GCTGTCGATGTAGC
536.	TGF-β2-18	CCAGGTTCTGCTTTATGG
537.	TGF-β2-19	CAGCAGGGACAGTG
538.	TGF-β2-20	CTTGCTCTAGTCTTCAC
539.	TGF-β2-21	GCCATCAATACTG
540.	TGF-β2-22	GGTGCCATCAATAACC
541.	TGF-β2-23	CCACTGGTATATGTGG
542.	TGF-β2-24	GGACTTTATAGTTTCTG
543.	TGF-β2-25	CTCAAGTCTGTAGGAG
544.	TGF-β2-26	GGTCTGTTGTGACTC
545.	TGF-β2-27	CAATTATCCTGCACATTTC
546.	TGF-β2-28	GCAGCAATTATCCTGC
547.	TGF-β2-29	GGCAGCAATTATCC
548.	TGF-β2-30	GGTTCGTGTATCCATTCC
549.	TGF-β2-31	GCACAGAAGTTGGC
550.	TGF-β2-32	CCAGCACAGAAGTTGG
551.	TGF-β2-33	GTGCTGAGTGTCTG
552.	TGF-β2-34	CCTGCTGTCGTGAGTG
553.	TGF-β2-35	GCTCAGGACCCTGC
554.	TGF-β2-36	GCAGCAAGGAGAAGC
555.	TGF-β2-37	CCAATGTAGTAGAGAATGG
556.	TGF-β2-38	GCTGCATTGCAAG
557.	TGF-β2-N-1	AAAAAAAGAAATCAA
558.	TGF-β2-N-2	AAAAAAAGAAATCAA
559.	TGF-β2-N-3	AAAAAAAGAAATCAA
560.	TGF-β2-N-4	TAAAAAAAAGAAATCAA
561.	TGF-β2-N-5	ATAAAAAAAAGAAATCAA
562.	TGF-β2-N-6	AATAAAAAAAAGAAATCAA
563.	TGF-β2-N-7	GAATAAAAAAAAGAAAT
564.	TGF-β2-N-8	AGAATAAAAAAAAGAAAT
565.	TGF-β2-N-9	CAGAATAAAAAAAA
566.	TGF-β2-N-10	TCAGAATAAAAAAA
567.	TGF-β2-N-11	TTGTTTTAAAGT
568.	TGF-β2-N-12	AGTTGTTTTAAAA
569.	TGF-β2-N-13	AAGTTGTTTTAAAA
570.	TGF-β2-N-14	AAAGTTGTTTTAAAA
571.	TGF-β2-N-15	AAAAGTTGTTTTAAAA
572.	TGF-β2-N-16	AAAAGTTGTTTTAAAA
573.	TGF-β2-N-17	AAAAAGTTGTTTTAAAA
574.	TGF-β2-N-18	AAAAAAAGTTGTTTTAAAA
575.	TGF-β2-N-19	AAAAAAAGTTGTTTTAAA
576.	TGF-β2-N-20	TTTTTAAAGTG
577.	TGF-β2-N-21	TTTTTAAAGTG
578.	TGF-β2-N-22	ATTTTTAAAGTG
579.	TGF-β2-N-23	CATTTTTAAAGTG
580.	TGF-β2-N-24	GCATTTTTAAAGAA
581.	TGF-β2-N-25	TGCATTTTTAAAGAA
582.	TGF-β2-N-26	AGCTTATTTAAAT
583.	TGF-β2-N-27	AAGCTTATTTAAAT
584.	TGF-β2-N-28	TAAGCTTATTTAAAT
585.	TGF-β2-N-29	TGTAATTATTAGAT

586.	TGF-β2-N-30	ATGTAATTATTAGAT
587.	TGF-β2-N-31	TGATGTAATTATTA
588.	TGF-β2-N-32	ATGATGTAATTATTA
589.	TGF-β2-N-33	ATGGTATTATATAA
590.	TGF-β2-N-34	TATGGTATTATATAA
591.	TGF-β2-N-35	TTATGGTATTATATAA
592.	TGF-β2-N-36	TTTATGGTATTATATAA
593.	TGF-β2-N-37	ATTTATGGTATTATATAA
594.	TGF-β2-N-38	AATCATATTAGAAA
595.	TGF-β2-N-39	TTACAATCATATTA
596.	TGF-β2-N-40	TTTACAATCATATTA
597.	rb-1	GGCATGACGCCCTTC
598.	rb-2	GCATGACGCCCTTC
599.	rb-3	GCCTGACGAGAGGC
600.	rb-4	CTCAAGCCTGACGAG
601.	rb-5	CCACAGTTCTTTTC
602.	rb-6	GCTGCAATAAAGATACAG
603.	rb-7	GCTGCAATAAAGATAC
604.	rb-8	GGACACTGATTTCTATG
605.	rb-9	GCATTATCAACTTGG
606.	rb-10	ACTTTTAGCACCAATG
607.	rb-11	CCAAGAAACTTTAGCACC
608.	rb-12	CCAGATCATCTTC
609.	rb-13	AGTCAAGGACACATAG
610.	rb-14	TCTTGAGCAACATGG
611.	rb-15	GGGTATAACAGCTG
612.	rb-16	GAGGTGAACCATTAAATGG
613.	rb-17	TCTTCGTATCGTTAG
614.	rb-18	TGTTGGATAGTGTTC
615.	rb-19	GTTGATCACTTGTG
616.	rb-20	GGATTCCATTACTCG
617.	rb-21	GACATATGAAAAATGTTGTC
618.	rb-22	GCCAATAAAGACATATG
619.	rb-23	CCAGAACATCAAGATCTG
620.	rb-24	CTGTTCCAGAACATCAAG
621.	rb-25	GACAAATCTGTTCCAGAAC
622.	rb-26	GGAAAGACAAATCTGTTCC
623.	rb-27	GATTAAGAGGACAAAGC
624.	rb-28	GGAAGATTAAAGAGG
625.	rb-29	GCAGTGTGATTATCTGG
626.	rb-30	GGAGAAAGATACATATCTG
627.	rb-31	GGAGATCTTACAGG
628.	rb-32	GCATTGCACTAGAAC
629.	rb-33	CAGTGAAAGAGAGG
630.	rb-34	GCTAGCCGATACAC
631.	rb-35	GGAAGATCCTGTATGC
632.	rb-36	GCATGAGGAAGATCC
633.	rb-37	GGAGTCATTTTGTG
634.	rb-38	CCAATTGATACTAACATT
635.	rb-39	TCTTTGAGCACACG
636.	rb-40	CCTTCAGCACTTCTTTG
637.	rb-41	GGTTGCTTCCTTCAGC
638.	rb-42	CAGTGGTTAGGAG
639.	rb-43	CCTGAGATCCTCATTT
640.	rb-44	CCAAGGTCTGAGATCC
641.	rb-45	GGTGTACACAGTGTCC
642.	rb-N-1	TATCTTAATTCT
643.	rb-N-2	TCTTTGAAATATAA
644.	rb-N-3	TTCTTTGAAATATAA
645.	rb-N-4	TTTCTTTGAAATATAA
646.	rb-N-5	TTTTCTTTGAAATATAA
647.	rb-N-6	TTTTCTTTGAAATATAA
648.	rb-N-7	ATTTCTATGTTTT
649.	rb-N-8	TTAAAGAATTATG
650.	rb-N-9	GTAAAGAATTAT

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651.	rb-N-10	AGTTAAAGAATTTAT
652.	rb-N-11	AAGTTAAAGAATTTAT
653.	rb-N-12	TAAGTTAAAGAATTTAT
654.	rb-N-13	TTTAGTAAGTTAAA
655.	rb-N-14	TTTTAGTAAGTTAAA
656.	rb-N-15	ATTTCTTTAGTAA
657.	rb-N-16	AATTCTTTAGTAA
658.	rb-N-17	ATCAATTCTTTA
659.	rb-N-18	TATCAATTCTTTA
660.	rb-N-19	AATATATAAGTCA
661.	rb-N-20	AAATATATAAGTCA
662.	rb-N-21	CAAATATATAAGTT
663.	rb-N-22	TCAAATATATAAGTT
664.	rb-N-23	TGTCAAATATATAA
665.	rb-N-24	AATTATTTCAGTA
666.	rb-N-25	AATAAAAATGTGAT
667.	rb-N-26	TAATAAAAATGTGAT
668.	rb-N-27	TAGCTAATAAAAAT
669.	rb-N-28	TTAGCTAATAAAAAT
670.	rb-N-29	TTTAGCTAATAAAAAT
671.	rb-N-30	AATAAAAATAGTCAA
672.	rb-N-31	TAATAAAAATAGTCAA
673.	rb-N-32	TTAATAAAAATAGTCAA
674.	rb-N-33	TTTAATAAAAATAGTCAA
675.	rb-N-34	GTTTAATAAAAATAGT
676.	rb-N-35	AGTTTAATAAAAATAGT
677.	rb-N-36	GAGTTAATAAAAATA
678.	rb-N-37	AGAGTTTAATAAAAATA
679.	rb-N-38	AATAATTCTTGAT
680.	rb-N-39	TATATACATTCA
681.	rb-N-40	ATCTATATTACATT
682.	rb-N-41	ATAAACATTTC
683.	rb-N-42	AATAAACATTTC
684.	rb-N-43	AAATAAACATTTC
685.	rb-N-44	GAAATAAACATTTC
686.	rb-N-45	TGAAATAAACATTTC
687.	rb-N-46	TTGAAATAAACATTTC
688.	rb-N-47	TTTGAAATAAACATTTC
689.	rb-N-48	TTTTGAAATAAACATTTC
690.	rb-N-49	TTTTGAAATAAACATTTC
691.	rb-N-50	ATTTTGAAATAAACATTTC
692.	rb-N-51	AATTTTGAAATAAACATT
693.	rb-N-52	AAATTGGAAATAAACATT
694.	rb-N-53	AAAATTTGAAATAAACATT
695.	rb-N-54	TAAAATTTGAAATAAACAA
696.	rb-N-55	ATAAAATTTGAAATAAAC
697.	rb-N-56	TATAAAAATTTGAAATAAA
698.	rb-N-57	GTATAAAAATTTGAAAT
699.	rb-N-58	GGTATAAAAATTTT
700.	rb-N-59	AGGTATAAAAATTTT
701.	rb-N-60	AAGGTATAAAAATTTT
702.	rb-N-61	AAAGGTATAAAAATTTT
703.	rb-N-62	AAAAGGTATAAAAATTTT
704.	rb-N-63	TAAAAGGTATAAAAATTTT
705.	rb-N-64	ATAAAAGGTATAAAAATTTT
706.	rb-N-65	TTTAGAAAGATT
707.	rb-N-66	AAGATAAAATTCTT
708.	rb-N-67	TAAGATAAAATTCTT
709.	rb-N-68	TTAAGATAAAATTCTT
710.	rb-N-69	TTTAAGATAAAATTCTT
711.	rb-N-70	TTTTAAGATAAAATTCTT
712.	rb-N-71	TTTTTAAGATAAAATTCTT
713.	rb-N-72	ATTTTTAAGATAAAATTCTT
714.	rb-N-73	TATTTTTAAGATAAAATTCT
715.	rb-N-74	TTTATTTTAAGATAAAATT
716.	rb-N-75	TTTATTTTAAGATAAAATT
717.	rb-N-76	CTTTATTTTAAGATAAAATT

718.	rb-N-77	TCTTTATTTTAAGATAAAAT
719.	rb-N-78	ATCTTATTTTAAGATAAAA
720.	rb-N-79	ATCTTATTTTAA
721.	rb-N-80	GATCTTATTTTAA
722.	rb-N-81	AGATCTTATTTTAA
723.	rb-N-82	TAGATCTTATTTTAA
724.	rb-N-83	AATCATCATTAAATT
725.	rb-N-84	AAATCATCATTAAATT
726.	rb-N-85	AAAATCATCATTAAATT
727.	rb-N-86	AAAATCATCATTAAATT
728.	rb-N-87	TTAAAATCATCATTAAATT
729.	rb-N-88	TTTAAAATCATCATTAAATT
730.	rb-N-89	ATTTAAAATCATCATTAAATT
731.	rb-N-90	AATTTAAAATCATCATTAA
732.	rb-N-91	GAATTAAAATCAT
733.	rb-N-92	TGAATTAAAATCAT
734.	rb-N-93	TTAAAATAGGAAAT
735.	rb-N-94	AATTTCCTTTAA
736.	rb-N-95	AAATTTCCTTTAA
737.	rb-N-96	TAAAATTGAAATG
738.	rb-N-97	CTAAAATTGAAAT
739.	rb-N-98	TTTGCTAAAATT
740.	rb-N-99	ATATGAAAAATGTT
741.	rb-N-100	TTTTAAATTAAAGCA
742.	rb-N-101	TTGTAAAAATCAA
743.	rb-N-102	TTTGTAAAAATCAA
744.	rb-N-103	TTTGATAAAACTT
745.	rb-N-104	ATGTTTATCATT
746.	rb-N-105	AATGTTTATCATT
747.	rb-N-106	AAATGTTTATCATT
748.	rb-N-107	AAATGTTTATCATT
749.	rb-N-108	TCTAAATGTTTAT
750.	rb-N-109	TTCTAAATGTTTAT
751.	rb-N-110	TAAGATCAAATAA
752.	rb-N-111	ATAAGATCAAATAA
753.	rb-N-112	AATAAGATCAAATAA
754.	rb-N-113	TAATAAGATCAAATAA
755.	rb-N-114	TTAATAAGATCAAATAA
756.	rb-N-115	TTTAATAAGATCAAATAA
757.	rb-N-116	TTGTTTAATAAGAT
758.	rb-N-117	ATTGTTTAATAAGAT
759.	rb-N-118	TGATTGTTAATAA
760.	rb-N-119	TTGATTGTTAATAA
761.	rb-N-120	TTTGATTGTTAATAA
762.	rb-N-121	TTTTATAAAACAGT
763.	rb-N-122	TTTTATAAAACAGT
764.	rb-N-123	TTTTTTATAAAACAGT
765.	rb-N-124	CTTTTTATAAAACA
766.	rb-N-125	ACTTTTTATAAAACA
767.	rb-N-126	CACTTTTTATAAA
768.	rb-N-127	ACACTTTTTATAAAA
769.	rb-N-128	TACACTTTTTATAAAA
770.	rb-N-129	ATACACTTTTTATAAAA
771.	rb-N-130	ATTTTGAATTAAAG
772.	rb-N-131	GATTTTGAATTAA
773.	rb-N-132	TGATTTGAATTAA
774.	rb-N-133	ATGATTTGAATTAA
775.	rb-N-134	AATGATTTGAATTAA
776.	rb-N-135	ATAATAGAATCATA
777.	rb-N-136	TATAATAGAATCATA
778.	rb-N-137	TATAATAGAATCAT
779.	rb-N-138	TAATATAATAGAAT
780.	rb-N-139	ATACTATAATAGAAT
781.	rb-N-140	AATACTATAATAGAAT
782.	rb-N-141	AGAATACTATAATA
783.	rb-N-142	TAGAATACTATAATA
784.	rb-N-143	ATAGAATACTATAATA

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785.	rb-N-144	TATAGAATACTATAATA
786.	rb-N-145	TTATAGAATACTATAATA
787.	rb-N-146	AATATTTGTTTCA
788.	rb-N-147	AAATATTGTTTCA
789.	rb-N-148	AAAATATTGTTTCA
790.	rb-N-149	CAAAATATTTGTTTT
791.	rb-N-150	AAATTATATGGAA
792.	rb-N-151	TGAAATTTATATG
793.	rb-N-152	CTGAAATTTATAT
794.	rb-N-153	TCTGAAATTTATAT
795.	rb-N-154	TTCTGAAATTTATAT
796.	rb-N-155	ATCTGATTTATTT
797.	rb-N-156	AAGATATTAATGT
798.	rb-N-157	TGAAGATATTAAT
799.	rb-N-158	ATAAATAACAATGA
800.	rb-N-159	TATAAATAACAATGA
801.	rb-N-160	GTATAAAACAAT
802.	rb-N-161	TGTATAAAACAAT
803.	rb-N-162	TTGTATAAAACAAT
804.	rb-N-163	TCTTGATAAATAA
805.	rb-N-164	ATCTTGATAAATAA
806.	rb-N-165	AATCTTGATAAATAA
807.	rb-N-166	ACAACTTTTAAAT
808.	rb-N-167	TACAACCTTTTAAAT
809.	rb-N-168	TACAACCTTTTAAA
810.	rb-T-1	CGGGGGGTTTGGCGGCATG
811.	rb-T-2	TTTCGGGGGTTTGGCGGC
812.	rb-T-3	TCGGGGGGTTTGGCGGC
813.	rb-T-4	GGTGGCGGCCGTTTTCGGGGGT
814.	rb-T-5	CCGGGGGTTCCGCGGGCAGCG
815.	rb-T-6	CGGGGGTTCCGCGGGCG
816.	rb-T-7	GGCGCGGTGCCGGGGTTCCGC
817.	rb-T-8	GGAGGGGGCGGCCGGCGGTG
818.	rb-T-9	GGGGCGGCCGGCGGGCG
819.	rb-T-10	GGGGCGGCCGGCGGGCG
820.	rb-T-11	AGGGGGCCTGGTGAAG
821.	rb-T-12	TAGGGGGCCTGGTG
822.	rb-T-13	GTAGGGGGCCTGGT
823.	rb-T-14	GAGGTATTGGTGACAAGGTAGGGGC
824.	rb-T-15	TCTTCAGGGGTGAAATATAGATGTT
825.	rb-T-16	GGACTCTCAGGGGTG

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826 TCGGACTATA CTGC
827 CAGTTCCGGAC TATACT
828 AAGCCTAAGA CGCA
829 GCCCAAGTTC AACAA
830 TGAAAAGTCG CGGT
831 GGTAAATTAA GATGCCTC
832 TCTCTAAGAG CGCA
833 ACGTGAGGTT AGTTTG
834 CACGTGAGGT TAGT
835 CATAGAACAG TCCG
836 CAGTCATAGA ACAGTC
837 CTTTGCAAGTC ATAGAACAA
838 TGCAGTCATA GAAC
839 GGTCGTTTCC ATCT
840 CATAGAAGGT CGTTTC
841 CGTCATAGAA GGTC
842 CATCGTCATA GAAGG
843 GGACGGGAGG AACGAGGCAGT TGAG
844 TAGCCATAAG GTCC
845 GGTTACTGTA GCCA
846 GGTTACTGTA GCCA
847 AGTTCTTGGC GCGGAGGT
848 AGGTGAGGAG GTCCGAGT
849 TGGACTGGAT TATCAG
850 GTGGTGGTGA TGTGCCCG
851 TGTCACGTT TC
852 CTCATCTGTC ACGT
853 CGAAGCCCTC GGCAGAAC
854 GCGTGTTCAGT GCTGTGCAGT TCGG
855 CTGCCCGTT GACC
856 AGGTTTGCAGT AGAC
857 GGTTGAAGTT GCTG
858 CTGGGTTGAA GTTG
859 TGCTGCACGG GCATCTGCTG
860 GGCACTGTCT GAGGCTCCTC CTTCAAGG
861 ACTCCATGTC GATG
862 CTCTCCGCCT TGATCC
863 GTTCCTCATG CGCTTC
864 CTGAGCTTTC AAGG
865 GCGATTCTCT CCAGCTTCCT TTTTCG
866 CTGAGCTTTC AAGGTTTCA CTTTTCCCTC
867 TCCCTGAGCA TGTT
868 TCTGTTTAAG CTGTGC
869 CTTTCTGTTT AAGCTGTG
870 GGTTCATGAC TTTCTG
871 CGTGGTTCAT GACT
872 ACTGTTAACG TGGTTC
873 CCACTGTTAA CGTG
874 CCCACTGTTA ACGT
875 AGCATGAGTT GGCA
876 GCGTTAGCAT GAGT
877 GTTTGCAACT GCTG
878 CAAAATGTTT GCAACTGC

Fig. 4 - 1

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879 TCCATTTAG TGCACATC
880 CTGTTCCATT TTAGTGCA
881 GTGTATGAGT CGTC
882 CTGTGTATGA GTCG
883 CGTAGCTGTG TATG
884 TCGTGTAGAG AGAG
885 AGTTTGTAGT CGTGTAGA
886 GTTTGTAGTC GTGTAG
887 AGTTTGTAGT CGTG
888 GGAGTTTGTA GTCG
889 TCAGGAGTTT GTAGTC
890 GTTTCAGGAG TTTGTAGT
891 TCGGTTTCAG GAGT
892 TTGAGACTCC GGTA
893 ACCAGAAAAG TAGCTG
894 CCTGACCAGA AAAG
895 ATTCAAGGCGT TCCA
896 GGTAAAAGTA CTGTCC
897 GGGTAAAAGT ACTGTC
898 GCACCTCCAC CGCTGCCA
899 CTCCTGCTCC TCGGTGAC
900 GCTTGACAA AGCC
901 CTTGTGCAGA TCGT
902 TCATCTTGTG CAGATC
903 GTTCATCTTG TGCAGA
904 CGTGGTTCAT CTTG
905 TCACGTGGTT CATC
906 GGTTGGTGTA AACG
907 TACGAGCTCC CGGTCCCGAC
908 TAGCTGATGG TGTT
909 TCCTTGAAGG TGGA
910 TCTTCCATGT TGATGG
911 CTTTGATGCG CTCT
912 CTCCCACTTTG ATGC
913 GCTCCAGCTT CCGCTTCCGG CACTTGGTGG
914 GGCCTTGAGC GTCTTCACCT TGTCCCTCCAG
915 TGACCTTCTG TTTGAG
916 CATGACCTTC TGTTTG
917 GTCATGACCT TCTG
918 CGAGAACATC ATCG
919 GTAGTCTGCG TTGA
920 GCTGCAGCGG GAGGATGACG
921 AGTAAGAGAG GCTATC
922 GTAGTAAGAG AGGC
923 GGTAGTAAGA GAGG
924 GTGAGTGGTA GTAAGA
925 GTCCGTGCAG AAGTCCTG
926 GAATGAAGTT GGCACT
927 GGAATGAAGT TGGC
928 GGGAAATGAAG TTGG
929 GCTGCACCAAG CCACTCAGG TCCGGACTGG
930 TCATGGTCTT CACAAC
931 CAATGCTCTG CGCTCGGCCT CCTGTCATGG

932 CTAGAGTTCC TCAC
933 GAGTACGCTA GAGT
934 GAAAGAGTACG CTAG
935 CTGCTTCCCC CCCAGCCCC ACATTCCC
936 TTCATCCTCT GTACTGGGCT
937 GTTACGGATG TGCA
938 CAGTTACGGA TGTG
939 CCAGTTACGG ATGT
940 AGAGTCTGAG TTGG
941 GTGAGACTCA GAGT
942 TCTTAGGGTG AGAC
943 GAGAGTACTT CTTAGG
944 GGAAGAAACT ATGAGAGT
945 CTTAGGGAAG AAACTATG
946 CGGTAAGAAA CTTAGG
947 AGCATGCGGT AAGA
948 GTCTGAAAGC ATGC
949 AGAACAAAGA AGAGCC
950 CAAGAGAAC AAGAAGAG
951 CAGCAAGAGA ACAAAAG
952 TCCTCAGCAA GAGA
953 AGGTGTGACT TGCA
954 GAATAGGTGT GACTTG
955 CAGAATAGGT GTGACT
956 GCAGAATAGG TGTG
957 CAGTTGCAGA ATAGGT
958 GAAACCATT CTGACC
959 TGTGAAACCA TTTCTGAC
960 CACTGTGAAA CCATTCT
961 CCACTGTGAA ACCA
962 AGAACTGGCT CCTGCAGCTT CCCTGCTTCC
963 CACCTCCATT CACCC
964 CAGTAAAAGT GTCTGC
965 CGACATTCA GAAAAAGTG
966 GACCGACATT CAGT
967 CTTCTGGAGA TAACTAGA
968 CATCTTATTTC CTTCCCT
969 CAGCCATCTT ATTCCCT
970 TGCAGCCATC TTATTC
971 GAGTGTATCA GTCAG
972 GGAGTGTATC AGTC
973 CTTGGAGTGT ATCAGT
974 ACAGAGTACC TACC
975 CCAACTTTCC CTTAAG
976 CCTTATGCTC AATCTC
977 GTCTTACTCA AGGG
978 ACAGTCTTAC TCAAGG
979 CATAAGACAC AGTCTTAC
980 GAAAGCATAA GACACAGT
981 GGAAAGCATA AGACAC
982 AGGGATAAAG GAAAGC
983 CCTGTATACA GAGG
984 TGTCTCCTGT ATACAG

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985 CATCTTCTAG TTGGTC
986 CTCATCTTCT AGTTGG
987 CTTCTCATCT TCTAGTTG
988 CAAAGCAGAC TTCTCA
989 CTGCAAAGCA GACT
990 CTAGTTTTC CTTCTCCT
991 TCTAGTTTTT CCTTCTCC
992 CAGGATGAAC TCTAGT
993 TCGTAGAAGG TCGT
994 AGGGTTACTG TAGC
995 GTAGTGGTGA TGTG
996 CGTCGTAGAA GGTC
997 TTTCGTGCAC ATCC
998 AGTTTGTAGT CGTGAAGA
999 CGAGAACATC ATGG
1000 GTAGTAGGAA AGGC
1001 GGTAGTAGGA AAGG
1002 GGAATGGTAG TAGG
1003 GGTCAATTGAG AAGAG
1004 GCTAATGTTC TTGACC
1005 GCCAAGGTCTCAT
1006 GGAGTCTATCTCCA
1007 CCAAAGAACCTGACT
1008 CACATGCTTAGTGG
1009 CTCGTAAATGACCG
1010 AGGAATCTCGTAAATGAC
1011 CAGCAGCGATTCTAT
1012 GGAGATCATCAAAGGA
1013 CTCAGCAATGGTCA
1014 GATCTCGAACACCT
1015 CACAATCTCGATCTTCT
1016 CCTTCTTAAAGATTGGCT
1017 CACATACCAACTGG
1018 AGCTTGATGTGAGG
1019 GAAGTTGTAGCTTGATGT
1020 GCTTGAAGTTGTAGCT
1021 CTGCTTGAAGTTGTAG
1022 GACACAACTCCTCT
1023 TCCTTGTAGACACAAAC
1024 CTCGTTGTAGACAC
1025 GGTTAGCACACACT
1026 GGTAACGGTTAGCA
1027 CGTAACACATTAGAAGC
1028 CTCATCCGTAACAC
1029 CCGGTAAGTATTGTAGTT
1030 GGTGTATTCCTTGAC
1031 ACATACCAACTGGTGT
1032 GTCCCTATACGAAC
1033 TTCATGTCTG TGCC
1034 GTAGGTGAGT TCCA
1035 GTTGTGAGCG ATGA
1036 CATAGTTGTC CTCAAAGA
1037 GGCATAGTTG TCCT

Fig. 4 - 4

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1038 CATTGTCTAG CACG
1039 CTCCATTGTC TAGC
1040 GTATTGTTCA GCGG
1041 TCAAGATCTC TGTGAG
1042 CACAAAATCG TGTCTT
1043 TCCTTCCACA AAATCG
1044 GTGGAAGATG TCCT
1045 TCTTGTTGAA GATGTC
1046 TCTATCAGTG TGAGAG
1047 GGTTGGTGTG TATC
1048 ACATCGGAGA ACAG
1049 CCTTACACAT CGGA
1050 ACAATCCTCA GAACTC
1051 GCTCTGACAA TCCT
1052 TGGTTGAAGT GGAG
1053 CTGTGGTTGA AGTG
1054 GTTGTAGGTG ACCA
1055 CTGTGTTGTA GGTG
1056 GACTCAAACG TGTC
1057 CATGGACTCA AACG
1058 CGAATGTATA CCGG
1059 CCGAATGTAT ACCG
1060 GCCGAATGTA TACC
1061 GTAGTTGTAG GGAC
1062 TAGAAAGGTA GTTGTAGG
1063 GTAGAAAGGT AGTTGTAG
1064 CGTAGAAAGG TAGTTG
1065 CCGTAGAAAG GTAG
1066 GACCATAGCA CACT
1067 GGATATTGGC ACTG
1068 CCTGGATATT GGCA
1069 GCTCCCAAAG ATCT
1070 CCCATCAAAG CTCT
1071 CAAACACTTG GAGC
1072 GTCTCAAACA CTTGGA
1073 GAGTCTCAAA CACTTG
1074 GTAACCTGTG ATCTCT
1075 GGTAAACCTGT GATC
1076 GTATAGGTAA CCTGTG
1077 TGAGATGTAT AGGTAACC
1078 TGCTGAGATG TATAGG
1079 CCATGCTGAG ATGT
1080 GGATTACTTG CAGG
1081 TGTTATGGTG GATGAG
1082 GGTGTTATGG TGGA
1083 GCAGTTGACA CACT
1084 AGTACTCGGC ATTC
1085 CATTCACATA CTCCCT
1086 TCCAAAACAG GTCACT
1087 GGTCCCTTATA GTGG
1088 CAGAATGCCA ACCA
1089 ACGAGAATGC CAAC
1090 GATCCCAAAG ACCA

1091 TCGCTTGATG AGGA
1092 CATCGTGTAC TTCC
1093 GCATCGTGT A CTTC
1094 ACTGTGCCAA AAGC
1095 CTTGTAGACT GTGC
1096 CCCTTGTAGA CTGT
1097 TCAACACTTT GATGGC
1098 CCCCTAACAC TTTG
1099 GTGTTTCCC TCAACA
1100 GTATGCTTCG TCTAAG
1101 CGTATGCTTC GTCT
1102 CCATCACGTA TGCT
1103 GCATAAGCTG TGTC
1104 CATGGTCTAA GAGG
1105 CAATCTGCAT ACACCA
1106 GGCATCTGC ATAC
1107 CTGTCTCGTC AATG
1108 CATAACTCCA CACATC
1109 AGTCACACCA TAACTC
1110 ACAGTCACAC CATAAC
1111 CCCCCAAAAGT CATC
1112 TCGTAAGGTT TGGC
1113 GATCCCATCG TAAG
1114 CAATGGTGCA GATG
1115 GACATCAATG GTGC
1116 GTAGACATCA ATGGTG
1117 CATGATCATG TAGACATC
1118 CCATGATCAT GTAGAC
1119 CATTGACCA TGATCATG
1120 CCAACATTTG ACCATG
1121 TCATCCAACA TTTGACCA
1122 GAGTCAATCA TCCAACAT
1123 CAGAGTCAAT CATCCA
1124 CCGACATTCA GAGT
1125 GAATTCAAGAC ACCAAC
1126 GATGACCACA AAGC
1127 CCATCAAATA CATCGG
1128 TCACCACCAA ATACATCG
1129 CAACGTAGCC ATCA
1130 ACGTCTTG A CGAC
1131 CAAAAACGTC TTTGACGA
1132 GGCAAAACG TCTTTG
1133 CAAAGGCAAA AACGTC
1134 GTGTCAAGTA CTCG
1135 GTAATAGAGG TTGTCG
1136 CCCAGTAATA GAGG
1137 CATGGTGCTC ACTG
1138 GTGCCTGTAC GTAC
1139 TGCAGGTGGA TAGT
1140 CATGTCGATA GTCTTGCA
1141 GTCGATAGTC TTGC
1142 CCATGTCGAT AGTC
1143 CTCCATGTGCG ATAG

1144 CTTGGACAGG ATCT
1145 TGCTGTTGTA CAGG
1146 GTGCTGTTGT ACAG
1147 TTGGCGTAGT AGTC
1148 TCCACCATTA GCAC
1149 GATTTCGTTG TGGG
1150 GTCATAGATT TCGTTGTG
1151 TGTACTCTGC TTGAAC
1152 GTGTACTCTG CTTG
1153 TGCTGTGTGT ACTC
1154 CTGATGTGTT GAAGAAC
1155 CTCTGATGTG TTGAAG
1156 GCTCTGATGT GTTG
1157 GAGCTCTGAT GTGT
1158 CACTTTAAC TTGAGCCT
1159 CTCCACTTT AACTTGAG
1160 TGCTGTATTT CTGGTACA
1161 CCAGGAATTG TTGC
1162 TTGCTGAGGT ATCG
1163 GATAACCACT CTGG
1164 CAAAAGATAA CCACTCTG
1165 CGGTGACATC AAAAG
1166 CCTCAATTTC CCCT
1167 GTTATCCCTG CTGT
1168 GCAGTGTGTT ATCC
1169 GATGTCCACT TGCA
1170 TAGTGAACCC GTTG
1171 TGCCATGAAT GGTG
1172 GTTCATGCCA TGAATG
1173 CATGAGAAC AGGA
1174 GCTTGCGAGA TGCT
1175 GAGCTTGCA GATG
1176 TAGTTGGTGT CCAG
1177 CTGAAGCAAT AGTTGG
1178 AGCTGAAGCA ATAGTTGG
1179 GGAGCTGAAG CAAT
1180 CAATGTACAG CTGC
1181 GGAAGTCAAT GTACAG
1182 CGGAAGTCAA TGTAC
1183 GCGGAAGTCA ATGT
1184 AGTTGGCATG GTAG
1185 GCAGAAAGTTG GCAT
1186 CTCAAATGT AGGG
1187 ACCTTGCTGT ACTG
1188 TGCTGGTTGT ACAG
1189 GGTTATGCTG GTTG
1190 GTAGTACACG ATGG
1191 CGTAGTACAC GATG
1192 CACGTAGTAC ACGA
1193 CATGTTGGAC AGCT
1194 GCACGATCAT GTTG
1195 CACACAGTAG TGCA
1196 GATCAGAAAA GCGC

1197 ACCGTGACCA GATG
1198 GTAGACAGGC TGAG
1199 TATCGAGTGT GCTG
1200 TTGCGCATGA ACTG
1201 TTGCTCAGGA TCTG
1202 ACTGGTGAGC TTCA
1203 GCTCAGGATA GTCT
1204 TGTAGATGGA AATCACCT
1205 TGGTGCTGTT GTAG
1206 TTCTCCTGGA GCAA
1207 TACTCTTCGT CGCT
1208 CTTGGCGTAG TACT
1209 CGGCATGTCT ATTTTGTA
1210 CGGGATGGCA TTTT
1211 CTGTAGAAAG TGGG
1212 ACAATTCTGA AGTAGGGT
1213 ATTGCTGAGA CGTCAAAT
1214 TCTCCATTGC TGAG
1215 TCACCAAATT GGAAGCAT
1216 CTCTGAACTC TGCT
1217 AACGAAAGAC TCTGAAC
1218 TGGGTTCTGC AAAC
1219 CTGGCTTTG GGTT
1220 GTTGTTCAGG CACT
1221 TCTGATATAG CTCAAATCC
1222 TCTTTGGACT TGAGAAC
1223 TGGGTTGGAG ATGT
1224 TGCTGTCGAT GTAG
1225 ACAACTTTGC TGTCGA
1226 ATTGCGCTTC TGCT
1227 GAAGGAGAGC CATT
1228 TCAGTTACAT CGAAGG
1229 TGAAGCCATT CATGAACA
1230 TCCTGTCTTT ATGGTG
1231 AAATCCCAGG TTCC
1232 GGACAGTGTA AGCTTATT
1233 GTACAAAAGT GCAGCA
1234 TAGATGGTAC AAAAGTGC
1235 CACTTTATT TGGGATGATG
1236 GCAAATCTTG CTTCTAGT
1237 GTGCCATCAA TACC
1238 GGTATATGTG GAGG
1239 TCTGATCACC ACTG
1240 TCCTAGTGGA CTTTATAG
1241 TTTTCCTAG TGGACT
1242 CAATAACATT AGCAGG
1243 AAGTCTGTAG GAGG
1244 TCTGTTGTGA CTCAAG
1245 GTTGGTCTGT TGTG
1246 CAAAGCACGC TTCT
1247 TTTCTAAAGC AATAGGCC
1248 GCAATTATCC TGCACA
1249 ACGTAGGCAG CAAT

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1250 ATCAATGTAA AGTGGACG
1251 CTAGATCCCT CTTG
1252 CCATTTCCAC CCTA
1253 TGGGTTCGTG TATC
1254 TGGCATTGTA CCCT
1255 TCCAGCACAG AAGT
1256 ATAATAACGG GCATGC
1257 AGTGTCTGAA CTCC
1258 TGTGCTGAGT GTCT
1259 ATAAGCTCAG GACC
1260 AGGAGAAGCA GATG
1261 AGCAAGGAGA AGCA
1262 AATCTTGGGA CACG
1263 TAGAGAATGG TTAGAGGT
1264 GTTTGCCAA TGTAGTAG
1265 CTTGGGTGTT TTGC
1266 GCAAGACTTT ACAATC
1267 GCATTTGCAA GACTTTAC
1268 TTTAGCTGCA TTTGCAAG
1269 GCCACTTTTC CAAG
1270 TTGGTCTTGC CACT
1271 CAGCACACAG TAGT
1272 CGATAGTCTT GCAG

1273	TGF- β 2-14/1	25 / ³⁶ CTTTCACCAAATTGGAAG
1274	TGF- β 2-14/2	CACCAAATTGGAAGC
1275	TGF- β 2-14/3	TCACCAAATTGGAAGC
1276	TGF- β 2-15/1	CTCTGGCTTTGGG
1277	TGF- β 2-9/1	CGGCATGTCTATTG
1278	relA-1	CACTACAGACGAGC
1279	relA-2	CGTGCACTACAGACG
1280	relA-3	GGAACAGTTCGTCC
1281	relA-4	GAACAGTTCGTCCATG
1282	relA-5	CCAGAGTTTCGGTTC
1283	relA-6	CTAGGACTGGGACAG
1284	relA-7	CGCACTTGTAGCG
1285	relA-8	CTCGCACTTGTAGC
1286	relA-9	GCACTTGTAGC
1287	relA-10	GCGCACTGTCCCTG
1288	relA-11	CCAGGGAGATGCGC
1289	relA-12	GCCGGTGAGGAGGG
1290	relA-13	CCGGTGAGGAGGG
1291	relA-14	CGGTTCACTCGGC
1292	relA-15	GAGTTTCGGTTCACTC
1293	relA-16	GGCACGATTGTCAAAG
1294	relA-17	CAGGCGTCACCCCC
1295	relA-18	GCAGGCGTCACCC
1296	p105/p50-1	CTCCCTCCTAAGC
1297	p105/p50-2	CCCTCCTAACCGG
1298	p105/p50-3	CGAGTCCCGCGTCG
1299	p105/p50-4	CATCTTCTGCCATT
1300	p105/p50-5	GTGTTTCCCACCAG
1301	p105/p50-6	GGTTTGGTTCACTAG
1302	p105/p50-7	GCATCTTCACGTCTCC
1303	p105/p50-8	CTTCACGTCTCCTGTC
1304	p105/p50-9	GTCACCGCGTAGTC
1305	p105/p50-10	CAAATAGGCAAGGTC
1306	p105/p50-11	CTTGCAAATAGGCAAG
1307	p105/p50-12	TGCTTGCAAATAGG
1308	p105/p50-13	CTGCTTGCAAATAGG
1309	p105/p50-14	GCAGGTGGATATT
1310	p105/p50-15	CTGCTGTTGGCAG
1311	p105/p50-16	CACTAGTTCCAAGT
1312	p105/p50-17	GTTTGGTTCACTAG
1313	p105/p50-18	CTTGATTCAGGATAG

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1314	p105/p50-19	GCACTTCTTCTTTATCT
1315	p105/p50-20	CCAAGTCAGATTCC
1316	p105/p50-21	GTTCCAAGTCAGATTTC
1317	p105/p50-22	GGTCACTAGTTCC
1318	p105/p50-23	GGTTTGGTCACTAG
1319	p105/p50-24	CCGAAAAATTGGGCA
1320	p105/p50-25	CCGAAAAATTGGG
1321	p105/p50-26	CTATCCGAAAAATTGG
1322	p105/p50-27	GTTGATAATGTCATCAG
1323	p105/p50-28	CTCATGTTGATAATGTC
1324	p105/p50-29	CTGTCACCGCGTAG
1325	p105/p50-30	CGTCTCCTGTCACCG
1326	p105/p50-31	CTTCACGTCTCCTG
1327	p105/p50-32	GAGAACCTTATCATGTC
1328	p105/p50-33	GCTATATGCAGGG
1329	p105/p50-34	CCAGCTGCTATATGCAGG
1330	p105/p50-35	AGGCTAAATTTGCCT
1331	p105/p50-36	GGCTAAATTTGCC
1332	p105/p50-37	GGCTAAATTTGCCTTC
1333	p105/p50-38	GCAGGCTAAATTTGCC
1334	p105/p50-39	GAGTTACCCAAGCG
1335	p105/p50-40	CAGAGTTACCCAAGCG
1336	p105/p50-41	CAGAGTTACCCAAG
1337	p105/p50-42	ACAGAGTTACCCAAG
1338	p105/p50-43	GGTGCAAAACAGAG
1339	p105/p50-44	CTAGGTGCAAAACAG
1340	p105/p50-45	GAGAACCTTATCATGTCC
1341	p105/p50-46	GCTAGATGAATGGC
1342	p105/p50-47	GCAAACATGGCAGGC
1343	p105/p50-48	CAGCAAACATGGCA
1344	p105/p50-49	GCAGCAAACATGGC
1345	p105/p50-50	AGCAGCAAACATGG
1346	p105/p50-51	CAGCAGCAAACATG
1347	p105/p50-52	AGCAGCAGCAAACA
1348	p105/p50-53	CAGCAGCAGCAAACA
1349	p105/p50-54	CAGCAGCAGCAAAC
1350	p105/p50-55	CACCAGCAGCAGCA
1351	p105/p50-56	GCATTGACGTCAAGC
1352	p105/p50-57	GATGTTGTCGTGCTC
1353	p105/p50-58	TGAGATGTTGTCGTGCT
1354	p105/p50-59	TGAGATGTTGTCGTG

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1355	p105/p50-60	GCCAATGAGATGTTG
1356	p105/p50-61	CTGCCAATGAGATG
1357	p105/p50-62	CACATGGGCATCAC
1358	p105/p50-63	TGTCCACATGGGCA
1359	p105/p50-64	GTACTGTCCACATG
1360	p105/p50-65	CAGCTGCTATATGC
1361	p105/p50-66	GTTCTCCACCAGGG
1362	p105/p50-67	AGTTCTCCACCAGG
1363	p105/p50-68	CAAAGTTCTCCACCAG
1364	p105/p50-69	CCAAGAGTCATCCAGG
1365	p105/p50-70	CCCAAGAGTCATCC
1366	p105/p50-71	CCTGCATTTCCCAAG
1367	p105/p50-72	TCCTGCATTTCCC
1368	p105/p50-73	GCCATATCTAGAGGC
1369	p105/p50-74	TCACATCTTCAGCC
1370	p105/p50-75	GCTTCACATCTTCAGC
1371	p105/p50-76	CAGCTTCACATCTTC
1372	p105/p50-77	GTAAC TTATA CAGCTGC
1373	p105/p50-78	CCAGTTTTGTCTGG
1374	p105/p50-79	CCATTGTCAGG
1375	p105/p50-80	GTGTAGCCCATTG
1376	p105/p50-81	GCTTCGGTAGCC
1377	p105/p50-82	GATCACTTCAATTGCTTC
1378	p105/p50-83	CTTGTGGAGGCAGG
1379	p105/p50-84	GCTGCCTGTGGAG
1380	p105/p50-85	CTATTGCTGCCTTGTGG
1381	p105/p50-86	GGATGTCTCCACGC
1382	p105/p50-87	GGAAGGATGTCTCC
1383	p105/p50-88	TGCGGAAGGATGTC
1384	p105/p50-89	GTTTGCAGGAAGGATGTC
1385	p105/p50-90	GCTGAGTTGCGGA
1386	p105/p50-91	GGTAAAGCTGAGTTG
1387	p105/p50-92	TCGGTAAAGCTGAG
1388	p105/p50-93	GACTCGGTAAAGCTG
1389	p105/p50-94	AGAGACTCGGTAAAGC
1390	p105/p50-95	GAAATTGTCAGCAGGC
1391	p105/p50-96	GAAATTGTCAGCAGG
1392	p105/p50-97	GGAAATTGTCAGCAGG
1393	p105/p50-98	GGAAATTGTCAGCAG
1394	p105/p50-99	GGGAAATTGTCAGC
1395	p105/p50-100	GTGTGGAAAATTGTC

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1396	p105/p50-101	GGTTTACACGGTGTG
1397	p105/p50-102	GCTTTGGTTTACACG
1398	p105/p50-103	GCACCTTGGAATGC
1399	NFKB2-1	CCAGGTTCTGCTTCC
1400	NFKB2-2	GCTCTGTCTAGTGGC
1401	NFKB2-3	ACTCTCCATGTCTC
1402	NFKB2-4	CAACTCTCCATGTCTC
1403	NFKB2-5	CAACTCTCCATGTC
1404	NFKB2-6	AGCAACTCTCCATG
1405	NFKB2-7	GTAGCAACTCTCCATG
1406	NFKB2-8	GTAGCAACTCTCCA
1407	NFKB2-9	GGTTGTAGCAACTCTCC
1408	NFKB2-10	CGGGCAGTCCTCCA
1409	NFKB2-11	GCACCGGGCAGTC
1410	NFKB2-12	AGGCACCAGGGCAG
1411	NFKB2-13	GTGTGTTACCAGGT
1412	NFKB2-14	TGTGTGTTACCAGGT
1413	NFKB2-15	TGGGTCACTGTGTG
1414	NFKB2-16	CAGACTGTGGGCATG
1415	NFKB2-17	CCCACCAAGACTGTGGG
1416	NFKB2-18	CCACCAAGACTGTGG
1417	NFKB2-19	TGCCCAACCAGACTG
1418	NFKB2-20	CGGCTTCCTCCCC
1419	NFKB2-21	CCTTGTCTTCCACC
1420	NFKB2-22	ACCGAGGCTGCCAC
1421	NFKB2-23	GGAAGAAACCGAGG
1422	NFKB2-24	GGGAAGAAACCGAG
1423	NFKB2-25	GGCCATCTGCGCC
1424	NFKB2-26	GCGGCCATCTGCG
1425	NFKB2-27	GTGGCGGCCATCTG
1426	NFKB2-28	ACCGTGGCGGCCAT
1427	NFKB2-29	GCCGCTCAATCTTCATC
1428	NFKB2-30	CTTCATCTTGTGATAGG
1429	NFKB2-31	GCTCAATCTTCATCTG
1430	NFKB2-32	CAGAAACACTGTTACAG
1431	NFKB2-33	CAGTTGCAGAACACTG
1432	NFKB2-34	GTTTCAGTTGCAGAAC
1433	NFKB2-35	CTTCCACCAGAGGG
1434	NFKB2-36	GTCTTCCACCAGAG
1435	NFKB2-37	CTTGTCTTCCACCAGAG
1436	NFKB2-38	TCCTTGTCTTCCAC

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1437	NFKB2-39	CTTCCTTGTCTTCCAC
1438	NFKB2-40	CATCTTGTGATAGGG
1439	NFKB2-41	GCTAGGTGCAGTGGT
1440	NFKB2-42	GATGGCTAGGTGCA
1441	NFKB2-43	GTGGATGATGGCTAG
1442	NFKB2-44	CCCGTGGATGATGG
1443	NFKB2-45	CTGCCCGTGGATGA
1444	NFKB2-46	AGAGCCTCCACCCA
1445	NFKB2-47	GTTGTACTCTCGAGC
1446	NFKB2-48	CGTTGTACTCTCG
1447	NFKB2-49	CGCGTTGTACTCTC
1448	NFKB2-50	GAGTCTCCATGCCG
1449	NFKB2-51	CTGAGTCTCCATGC
1450	NFKB2-52	CATGGCTGAGTCTC
1451	NFKB2-53	TGCATGGCTGAGTC
1452	NFKB2-54	GCGTTCACGTTGGC
1453	NFKB2-55	GTGCGAGCGTTCAC
1454	NFKB2-56	AGGTGCGAGCGTTTC
1455	NFKB2-57	GCAAAGGTGCGAGC
1456	NFKB2-58	CCTGGTGGCTCAGG
1457	NFKB2-59	GTCAGTCACCTGAG
1458	NFKB2-60	CAGGTCAGTCACCTG
1459	NFKB2-61	CAGCAGGTCA GTCAC
1460	NFKB2-62	GCAGCAGGTCA GTTC
1461	NFKB2-63	CATTAGCAGCAAGGTC
1462	NFKB2-64	GCAGCATTAGCAGC
1463	NFKB2-65	CTGAGCAGCATTAG
1464	NFKB2-66	CCCATGAGAATCCT
1465	NFKB2-67	CCTTCCCATGAGAATCC
1466	NFKB2-68	TCCTCCCCTTCCCA
1467	NFKB2-69	GCCTCCAGTAGACC
1468	NFKB2-70	GTCAGACAGGGCCT
1469	NFKB2-71	CCATGTCAGACAGG
1470	NFKB2-72	GGCCCATGTCAGAC
1471	TANK-1	GCTATTCTGAAATCAC
1472	TANK-2	CCTCTTGTCTTCTTACC
1473	TANK-3	GGAGAAGAAACCTCTTG
1474	TANK-4	CCTTGCTGAAGTTCTT
1475	TANK-5	CCAAGACTCCTTGC
1476	TANK-6	CCCTTTCATGGAGC
1477	TANK-7	CCTCTTGGTGTGAC

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1478	TANK-8	GACTAAGGATGCCG
1479	TANK-9	GTGGCAGGACTAACGG
1480	TANK-10	AGACGTGGCAGGAC
1481	I-kappa-Bepsilon-1	CTTCCAGCAGGCAG
1482	I-kappa-Bepsilon-2	GTTCCCTCTGCCTGG
1483	I-kappa-Bepsilon-3	GATGTCCTCTGCCTG
1484	I-kappa-Bepsilon-4	GAGATGTCCTCTGCC
1485	I-kappa-Bepsilon-5	GTGAGATGTCCTCTG
1486	I-kappa-Bepsilon-6	CAGAGAGTGAGATGTTCC
1487	I-kappa-Bepsilon-7	CCAGAGAGTGAGATGTTCC
1488	I-kappa-Bepsilon-8	GGTCCAGAGAGTGAG
1489	I-kappa-Bepsilon-9	GAGGTCCAGAGAGTG
1490	I-kappa-Bepsilon-10	GGTCCTGTAGTGCC
1491	TRAF-6-1	GATTTATGATGCAGGC
1492	TRAF-6-2	GACCTGCATCCCTTATTG
1493	TRAF-6-3	TAGTTGATTTCCAGCAG
1494	TRAF-6-4	GAATCTCACGTTTGC
1495	TRAF-6-5	CAGAGAAAGAACATCTCACG
1496	TRAF-6-6	TTTCACCATTAGAGAAAG
1497	TRAF-6-7	CATTGGACATTCACC
1498	TRAF-6-8	CCTTCATTGGACATTTC
1499	TRAF-6-9	CAATGTGCTTGATGATCC
1500	Rank-1	CGCATCGGATTTC
1501	Rank-2	CAAACCGCATCGGATTTC
1502	Rank-3	GAAGTGCAAACCGC
1503	Rank-4	GCAGAGAAGAACTGC
1504	Rank-5	GCAAGTAAACATGGG
1505	Rank-6	GGTCCACGTTTGG
1506	Rank-7	GCAAGGGTCCACGTT
1507	Rank-8	TGGCTTCTCTTCAGGG
1508	Rank-9	TCCTGCTGGCTTCTTC
1509	Rank-10	GTCCTGCTGGCTTC
1510	IL-5-1	GGTAGTCTAGGAATTGG
1511	IL-5-2	CTTGCAGGTAGTCTAGG
1512	IL-5-3	GAAACTCTGCAGGTAG
1513	IL-5-4	CACCAAGAAACTCTTC
1514	IL-5-5	CATTACACCAAGAAACTC
1515	IL-5-6	CTCGGTGTTCAATTACACC
1516	IL-5-7	CTTTCTATTATCCACTCG
1517	IL-5-8	CCAGTTAGTCTCAACTT
1518	IL-5-9	AACCAGTTAGTCTAAC

1519	IL-5-10	ACAAACCAGTTAGTCTC
1520	IL-13-1	CTCGCGAAAAAGTTTCTT
1521	IL-13-2	CCCTCGCGAAAAAGTTTC
1522	IL-13-3	GTCCCTCGCGAAAAAG
1523	IL-13-4	CAGTTGAACCGTCCC
1524	IL-13-5	GCTTCGAAGTTCAGTT
1525	IL-13-6	GATGCTTCGAAGTTTC
1526	IL-13-7	CTGTCTCTGCAAATAATG
1527	IL-15-1	CACTTATTACATTCACCC
1528	IL-15-2	TTTCCTCCAGTTCTC
1529	IL-15-3	GGACAATATGTACAAAAC
1530	IL-15-4	GTTGATGAACATTGGAC
1531	IL-15-5	GTGTTGATGAACATTGG
1532	I-kappaB(newmember)-1	CAAAATTGGCCAGGG
1533	I-kappaB(newmember)-2	GCCCCAAATTGGCC
1534	I-kappaB(newmember)-3	CCCAGCCCCAAATTGG
1535	I-kappaB(newmember)-4	GTCCCCAGCCCCAAATT
1536	I-kappaB(newmember)-5	AAATGCCAGAGGCTG
1537	I-kappaB(newmember)-6	ACCAAATGCCAGAGG
1538	I-kappaB(newmember)-7	CATCACCAAATGCCAG
1539	Prostaglan.Rec.EP3-1	TAGGAGTGGTTGAGGC
1540	Prostaglan.Rec.EP3-2	GTGTAGGAGTGGTTGAG
1541	Prostaglan.Rec.EP3-3	CTGTGTAGGAGTGG
1542	Prostaglan.Rec.EP3-4	CCCACATGCCTGTG
1543	Prostaglan.Rec.EP3-5	CGATGAACAACGAG
1544	Prostaglan.Rec.EP3-6	CTGGCGATGAACAAACG
1545	Prostaglan.Rec.EP3-7	CGCTGGCGATGAAC
1546	Prostaglan.Rec.EP3-8	GAGCTAGTCCCGTTG
1547	Prostaglan.Rec.EP3-9	GCGAAGAGCTAGTCC
1548	Prostaglan.Rec.EP3-10	CCAGTTATGCGAAGAGC
1549	Prostaglan.Rec.EP3-11	CCCCAGTTATGCGAAG
1550	PresenilinI-1	CACATGCTTGGCGC
1551	PresenilinI-2	GATCACATGCTTGGCG
1552	PresenilinI-3	GACAAAGAGCATGATCAC
1553	PresenilinI-4	GAGTCACAGGGACAAAG
1554	PresenilinI-5	GAGAGTCACAGGGAC
1555	PresenilinI-6	GCAGAGAGTCACAGG
1556	PresenilinI-7	CCATGCAGAGAGTC
1557	PresenilinI-8	CCACCATGCAGAGAG
1558	PresenilinI-9	TAGCCACGACCACC
1559	PresenilinI-10	GATTAGCTGCCATCCTT

1560	PresenilinI-11	GGTATAGATTAGCTGCC
1561	PresenilinI-12	GTATCTTCTGTGAATGGG
1562	PresenilinI-13	CTGGCCCACAGTCT
1563	PresenilinI-14	CTCTGGCCCACAGT
1564	PresenilinI-15	TGCAGGGCTCTCTG
1565	PresenilinI-16	AGTGCAGGGCTCTC
1566	PresenilinI-17	CACTGATCATGATGGC
1567	PresenilinI-18	GACACTGATCATGATGGC
1568	PresenilinI-19	ACAATGACACTGATCATG
1569	PresenilinI-20	GAACCACCAGGAGGAT
1570	PresenilinI-21	GACACAAAACAGCCACT
1571	PresenilinI-22	GTGGACCTTCGGAC
1572	PresenilinI-23	CAACCAGCATACGAAGT
1573	PresenilinI-24	TCCCTCTGGGCTTC
1574	PresenilinI-25	ACTGTCCCTCTGGG
1575	PresenilinI-26	GAUTGTCCCTCTGG
1576	PresenilinI-27	CCTAGATGACTGTCCC
1577	PresenilinI-28	CAGCGAGGATACTGC
1578	PresenilinI-29	CTTCACCAGCGAGGAT
1579	PresenilinI-30	TTTCCTCTGGGTCTTCAC
1580	PresenilinI-31	CTTTCCTCTGGGTCTTC
1581	PresenilinI-32	CTCCCAATCCAAGTTT
1582	TRADD-1	TTCATCCCGGAGCC
1583	TRADD-2	TTCTTCATCCCGGAGC
1584	TRADD-3	GCTCAGCCAGTTCTTC
1585	TRADD-4	GACAGAGAGGGCAC
1586	TRADD-5	CTTCACCTCCGACAG
1587	TRADD-6	GAAAAGTCTGGGCAGG
1588	TRADD-7	GACCCTGGAACAGAAAAG
1589	TRADD-8	CTGACCCTGGAACAG
1590	TRADD-9	ACTACAGGCTGACCT
1591	TRADD-10	ATTCACTACAGGCTGACC
1592	TRADD-11	CGATTCACTACAGG
1593	TRADD-12	GGCCGATTCACTAC
1594	TRADD-13	CGAACGTCTGTTGGTC
1595	TRADD-14	CGCGAACGTCTGTTG
1596	PKA-1	CTTCTGTTGTCGAGGAT
1597	PKA-2	TTCACCACCTCTGTTG
1598	PKA-3	AGGATGCCTTTCATT
1599	PKA-4	AGCTTGCAGGATGCG
1600	PKA-5	GTTGACAGCTTGCAAGGAT

1601	PKA-6	GGAACGGAAAGTTGACAG
1602	PKA-7	AACTCGAGTTGACGAGG
1603	PKA-8	TGTCCCTGAAGGAGAAC
1604	PKA-9	CGTACTCCATGACCATGT
1605	PKA-10	GCACGTACTCCATGAC
1606	PKA-11	GATTCTCCGGCTTCAG
1607	PKA-12	TCAATGAGCAGATTCTCC
1608	PKA-13	GGTCAATGAGCAGATTTC
1609	PKA-14	CCCTGCTGGTCAATG
1610	PKA-15	TAGCCCTGCTGGTC
1611	PKA-16	CGCTTGGCGAAACC
1612	PKA-17	CCTTCACCGCGCTTG
1613	PKA-18	AAGGTCCAAGTGCG
1614	PKA-19	TGCCGCACAAGGTC
1615	IL-12alpha-1	GGTGAGGACCACCATT
1616	IL-12alpha-2	GGGTGTCACAGGTG
1617	IL-12alpha-3	ATACCATCTTCTTCAGGG
1618	IL-12alpha-4	GGTGATACCATCTTCTTC
1619	IL-12alpha-5	CCAGGTGATACCATCTTC
1620	IL-12alpha-6	CCTCACTGCTCTGGT
1621	IL-12alpha-7	TAAGACCTCACTGC
1622	IL-12alpha-8	CAGAGCCTAACGACCTC
1623	IL-12alpha-9	CCAGAGCCTAACGACC
1624	IL-12alpha-10	TCTTCCTTTGTGAAGC
1625	IL-12alpha-11	GACCAAATTCCATCTTCC
1626	IL-12alpha-12	ATCAGTGGACCAAATTCC
1627	IL-12alpha-13	GGTTCTTCTGGTCCTTT
1628	IL-12alpha-14	TTTTGGGTTCTTCTGG
1629	IL-12alpha-15	GGTCTTATTTTGGGTTTC
1630	IL-12alpha-16	AATGGGCAGACTCTCCT
1631	IL-12alpha-17	TCCACCATGACCTCAATG
1632	IL-12alpha-18	AACGGCATCCACCATG
1633	IL-12alpha-19	GTGAACGGCATCCAC
1634	IL-12alpha-20	ACTTGAGCTTGTGAACGG
1635	IL-12alpha-21	TTCATACTTGAGCTTGTG
1636	IL-12alpha-22	CTGGTGTAGTTTCATAC
1637	IL-12alpha-23	AGCTGCTGGTGTAGTTT
1638	IL-12beta-1	AGGAGGACCAGGGT
1639	IL-12beta-2	AGGTGGTCCAGGAG
1640	IL-12beta-3	TTTCTGGCCAAACTGAGG
1641	IL-12beta-4	GGAGGTTCTGGCC

1642	IL-12beta-5	TCTGGAGTGGCCAC
1643	IL-12beta-6	CTTCTGGAGCATGTTGCT
1644	IL-12beta-7	GCCTTCTGGAGCATG
1645	IL-12beta-8	GTTTGTCTGGCCTCTG
1646	IL-12beta-9	GAGTTTGTCTGGCCTTCT
1647	IL-12beta-10	CTAGAGTTGTCTGGCCT
1648	IL-12beta-11	GCAAGGGTAAAATTCTAG
1649	IL-12beta-12	AGTGCAAGGGTAAAATTC
1650	IL-12beta-13	AAACAGGCCTCCACT
1651	IL-12beta-14	CTTGGTTAATTCCAATGG
1652	IL-12beta-15	AGGCAACTCCCATTAGTT
1653	IL-12beta-16	TACTACTAAGGCACAGGG
1654	IL-12beta-17	AATACTACTAAGGCACAG
1655	IL-12beta-18	GTACATCTCAAGTCTTC
1656	Pg-R	GGAGTGGACATGAT
1657	thr	AAGAAGATGAAGCCTTG
1658	ref-fosjun	CCGTCTTACTCTTCTTGG
1659	PIV	CCGATACAATTCCAAGG
1660	PIV	CCTTTCCCTCTGAG
1661	PIV	CTGTTGCAAGTACG
1662	bak	CAGAACGAGAGGGC
1663	bak	CCTCAGAACGAGAGG
1664	bak	CTCCTCAGAACGAG
1665	bak	ACAGGCTGGTGGCA
1666	bak	CCACTCTAAACAGGC
1667	bak	ACGGTAGCCGAAGC
1668	bak	GACGGTAGCCGAAGC
1669	bak	GGCCAGACGGTAGC
1670	bak	GTGTAGGGCCAGACGGTA
1671	bak	CCGAAGCCATTTTCAGG
1672	bak	CCCCGAAGCCATTTTC
1673	bak	GGTTGATGTCGTCC
1674	bax	GCTTGAGACACTCGC
1675	bax	CCGGACCCGTCCAT
1676	bclx	GCTTGCTTACTGC
1677	bclx	GGTTGCTCTGAGAC
1678	bclx	GCCACAGTCATGCC
1679	bmp	CGGGCATGCTGGCG
1680	bmp	GTGAAGTTCAAGGATGATC
1681	bmp	CCAGTGCCTCATGG
1682	ICE	CAGTGTCTCCATGG

1683	ICE	CTGTACCAGACCGAG
1684	ICE	GCATACTGTTTCAGC
1685	ich	GCCATCAGCTCCTTG
1686	ich	CCACACCATAAGATGG
1687	ich	GCTGGAGCAGTTCC
1688	bcl1	CTCGCTTCTGCTGC
1689	bcl2	AACCGTGGCAAAGCG
1690	mucrep	AGGTGACACCGTGG
1691	AHR	GACTTGATTCTTCAG
1692	AHR	GGATTGACTTGATTCC
1693	AHR	GCTGCTGTTCATGG
1694	AHR	CCGTTCTTCAGTAGG
1695	CD2	CTTGAAGTAGGAGC
1696	MEK2	CGCTCCTACATGGC
1697	tnf	GATGAGGTACAGGCC
1698	tnf	GTAGATGAGGTACAG
1699	tnf	GAGTAGATGAGGTAC
1700	tnf	CCTGGGAGTAGATG
1701	tnf	GGACCTGGGAGTAG
1702	tnf	ACATGGGTGGAGGG
1703	tnf	GTGCTCATGGTGTG
1704	tnf	CTTTCAGTGCTCATG
1705	tnf	TGCTTCAGTGCTCA
1706	tnf	GATGATCTGACTGCC
1707	tnf	GTTCGAGAAGATGATC
1708	tnf	GGGTCGAGAAGATG
1709	tnf	GGTTTGCTACAACATG
1710	tnf	CAGCTTGAGGGTTG
1711	tnf	TGCCCTCAGCTTG
1712	TNFR	GACACACACTATCTC
1713	IL-18	GCAGCCATCTTATTG
1714	IL-18	GTTCAGCAGCCATC
1715	IL-18	TGGTCAGCAGCCA
1716	IL-18	CTACTGGTTCAGCAGC
1717	IL-18	TCTACTGGTTCAGC
1718	IL-18	GCCACAAAGTTGATGC
1719	IL-18	CATTGCCACAAAGTTG
1720	IL-18	GAGAACTTGGTCATTC
1721	IL-18	GGTCAATGAAGAGAAC
1722	IL-18	CGATTTCCTGGTC
1723	IL-18	CCGATTTCCTGGTC

1724	IL-18	CAAATAGAGGCCGATTTC
1725	IL-18	CAAATAGAGGCCGA
1726	IL-18	CCTCTAGGCTGGCT
1727	IL-18	CATAACCTCTAGGCTG
1728	IL-18	AGCCATACCTCTAG
1729	IL-18	CAGCCATACCTCTAG
1730	IL-18	CACAGAGATAGTTACAG
1731	IL-18	GTCTCGTTTGAACAG
1732	IL-18	CTAGTCTCGTTTGAAC
1733	IL-18	TAGCTAGTCTCGTTTG
1734	IL-18	GAGCCACTGCGCC
1735	IL-18	CGTGAGCCACTGCG
1736	IL-12-Rec	CGTAACGATCACTGG
1737	IL-12-Rec	GCACTCGTAACGATC
1738	IL-12-Rec	GGAGCACTCGTAAC
1739	IL-12-Rec	CATCATCCTGAGGT
1740	IL-12-Rec	CAGTATCATCATCCTG
1741	IL-12-Rec	CTCAGTATCATCATCC
1742	IL-12-Rec beta2	CTAAAAGTATGTGCCATC
1743	IL-12-Rec beta2	CACATCGCCTCTCT
1744	IL-12-Rec beta2	GCTTCACAGTCACATCGC
1745	IL-12-Rec beta2	GGAAGGCTTCACAGTC
1746	IL-12-Rec beta2	CCTGTGACTTGAGAATTG
1747	IL-12-Rec beta2	GGAAGACCTGTGAC
1748	IL-12-Rec beta2	CTCTGCTCCAATATTG
1749	IL-12-Rec beta2	CAACGAAGATCTCTG
1750	IL-12-Rec beta2	CAACACCAACGAAG
1751	PKC-beta	GGTCTTCTGTTGC
1752	CB-1-Rec	CGATGAAGTGGTAGGAAG
1753	TGF-alpha	GGTTGCATGGAAGC
1754	Fascin	GGTCACAAACTTGCC
1755	p300	CTGATTGGTCCACTAG
1756	CBP	CATGTTAGCACTGTT
1757	rac-alpha	GGTCTTGATGTACTCC
1758	EBV	CCACCTAAAGAGAGATC
1759	HSPQ	CTTGTACTGCACCATC
1760	CC-CKR1	GCCAGTTAAGAAGATG
1761	CC-CKR4	GAGATCATGATCCATGG
1762	c-CRK	GTAGTGTCCAATAGTG
1763	c-CRK	CTTCCTCATCATTCCC
1764	CRKL	CACAAGCTTTCGAC